glial cells

Glial cells are maintenance and support cells in the central nervous system (CNS). They are 10 times as numerous as the nerve cells (neurons) which they look after and make up about half the wieght of the brain. There are a number of different types of glial cell in the CNS including: oligodendrocytes, astrocytes and microglia. Analogous cells in the Peripheral Nervous System (PNS) are Schwann and Satellite cells.

Not all the functions of glial cells are understood but some of their functions are:

- Repair and maintenance. Glial cells attempt to keep neurons heathly. They produce new myelin when it become damaged (oligodendroctyes) and lay down scar tissue (astroctyes).
- Physical support. Glial cells have hairlike filaments which hold the neurons in place and allow the central nervous system to retain its structural integrity (astrocytes).
- Central Nervous Sytem development. Glial cells provide an important function in the early and continuing development of the brain.
- Chemical regulation. Glial cells supply chemicals such as potassium and calcium and regulate neurotransmitter levels (astrocytes).
- Cleaning. Glial cells remove dead cells and other debris from the CNS (astrocytes and microglia).
- Isolation of the CNS. It used to be thought that glial cells were important to the Blood Brain Barrier (BBB) which shields the brain from invasion by pathogens and other unwanted cells. This function is now disputed and many neurologists now believe it is performed by the endothelial cells.

Glial cells, especially oligodendrocytes are often destroyed at the site of multiple sclerosis lesions. This postpones or even prevents the repair of the damaged myelin. Working out how to transport new oligodendrocytes to the site of lesions or growing new ones from stem cells is the focus of some of the reseach into new treatments for MS.

Glial cell links:
Neuroscience for Kids - Glia
Glial Cells
Glial cells and growth factors
Glial Cells and Multiple Sclerosis
Glial Cells
Protection of neurons by Glial Cells
Glial Cells
In vitro differentiation of embryonic stem cells into glial cells and functional neurons

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MS Glossary
Searchable MS Glossary
All About Multiple Sclerosis

Last Modified: Monday, May 06, 2002 09:58:07 AM

Science, 25. Feb 2000, Vol 287, No. 5457, page 1442

Translating Stem and Progenitor Cell Biology to the Clinic: Barriers and Opportunities

Stem cells are the natural units of embryonic generation, and also adult regeneration, of a variety of tissues. Recently, the list of tissues that use the model of differentiation from stem to progenitor to mature cell has increased from blood to include a variety of tissues, including both central and peripheral nervous systems and skeletal muscle; it is also possible that all organs -and tissues are derived from, and still contain, stem cells. Because the number and activities of stem cells and their progeny are homeostatically regulated, clinical stem cell transplantation could greatly add to the physician's armamentarium against degenerative diseases.

Irving L. Weissman

The clinical application of stem and progenitor cell transplantation began with the exposure of civilian populations to lethal doses of radiation in 1945. Irradiation of mice replicated the syndrome, and bone marrow (BM) transplants radioprotected them by providing donor-derived hematopoiesis (1-3). In 1961, Till and McCulloch demonstrated the existence of clonogenic BM precursors that give rise to multilineage hematopoietic colonies in the spleen [colony-forming units, spleen (CFU-S)]; a subset of spleen colonies contained cells capable of forming more spleen colonies. They proposed that these were pluripotent hematopoietic stem cells (HSCs) (4-6) that had the property, at the single-cell level, of (i) self-renewal as well as (ii) multilineage differentiation. This remains the enduring definition of stem cells.

Whereas the above-described experiments provided evidence that stem cells exist, they did not enable their isolation. With the development of quantitative assays for clonogenic precursors in mice of all hematolymphoid precursors (7-9), a reductionist approach was developed for the identification and isolation of HSCs. Monoclonal antibodies (mAb) were identified that bind cell surface markers on some, but not all hematopoietic cells; marker positive and negative subsets were separated by cell sorting (e.g., fluorescence-activated cell sorting) to identify cells with clonogenic precursor activity (9). Eventually, clonogenic multipotent progenitors with a distinctive marker profile proved to be HSCs (Fig. 1A) (10-13). A subset of this population perpetually self renews; these are long-term stem cells (LT-HSCs) (12, 14). All subsets of these HSCs were radioprotective, and HSCs were the only radioprotective elements in mouse bone marrow (11). As the HSC cell dose increased, the time to engraftment of clinically protective numbers of donor-derived blood cells shortened (Fig. 113) (15). Subsequently, in vitro and in vivo assays for clonogenic human stem and progenitor hematolymphoid cells were developed and by the same approach candidate human HSCs were isolated (16, 17).

The mouse and human HSCs depicted in Fig. 1A were the first isolated by surface markers. It was subsequently shown that both $CD34^+$ and very rare $CD34^-$ subsets of LT-HSCs exist (18, 19); HSCs actively extrude dyes such as Hoechst 33324 and Rhodamine 123, and can be isolated by this property (20). In humans, the mAb AC133 also identifies HSC (21).

Purified human HSCs are capable of hematopoietic reconstitution in patients receiving bone marrow ablative (myeloablative) doses of radiation and chemotherapy. Increasing the dose of HSC shortens the time to engraftment of mature blood elements in man as in mice (Fig. 1C) (22-24).

Biology of Hematopoietic Stem and Progenitor Cells

In mice, LT-HSCs give rise to short-term HSCs (ST-HSCs), which give rise to multipotent progenitors (MPPs), whose further progeny are oligolineage-restricted (Fig. 2) (12); dedifferentiation cannot be detected (25). HSCs can first be found in the developing yolk sac blood islands; transfer of blood island cells to same age-hosts resulted in lifelong, donor-derived hematopoiesis (26). HSCs can also be found

in the embryo proper (27, 28). HSC are next found in the fetal liver (13), and then the fetal spleen and BM (29); each stage occurs presumably by HSCs entering the fetal circulation. In young adult mice, about 8% of the LT-HSC population randomly enters cell division per day, and on average, half their progeny must be LT-HSCs to maintain the steady-state level. As HSCs progress to MPPs, the frequency of cells in cycle increases (30, 31). In very old mice, most LT-HSCs are in cycle (32).

Dividing HSCs have four developmental choices: self-renewal, differentiation, programmed cell death, and emigration (33). The frequency of HSCs in hematopoietic organs is regulated by the fraction of stem cells that choose one or another of these fates. Transgenic expression of the anti-programmed cell death gene bcl-2 (a proto-oncogene) in HSC results in an increase in their frequency in BM (34). These HSC have increased chemo- and radiotherapy resistance, a property that would be much valued clinically if bcl-2 expression could be regulated. The movement of stem cells between primary hematopoietic sites occurs naturally throughout life (35). Clinical provision of cytokines such as G-CSF alone or along with cytoreductive drugs [for review, see (36)] can induce mobilization of stem cells to blood (MPB), where they are collected for transplantation. Natural and induced HSC mobilization begins with mitotic expansion of HSC, followed by the release of G_1 HSC to blood to seed secondary sites (35).

Oligopotent progenitors downstream of HSCs have also been isolated (Fig. 2) (37, 38); HSC give rise alternatively to the clonal common lymphocyte progenitor (CLP), or the clonogenic common myeloid progenitor (CMP). CMP, in turn, can give rise to megakaryocyte or erythrocyte progenitors (MEPs), or granulocyte/monocyte progenitors (GMPs). None of these progenitors dedifferentiate or show self-renewal capacity (37, 38).

Broadening the Stem and Progenitor Cell Concept to Other Tissues

In vertebrates, the zygote is a totipotent stem cell, as are virtually all of its progeny around the blastula stage; cells contained within the inner cell mass (ICM), include (and may be composed of) totipotent stem cells (TSCs) (Fig. 3) (39). Embryonic stem (ES) cells are derived from cultures of ICM cells, and have the property of participating as totipotent cells when placed into host blastocysts. The developmental pathways that endogenous ICM cells or transferred ES cells take to tissue formation and organogenesis has led many to hope that these pathways can be controlled for the development of tissue and organ specific stem cells (40). However, we currently have an insufficient understanding of the developmental events that lead to organogenesis from ICM cells to program the production of tissue- or organ-specific stem cells.

During vertebrate development, at defined stages the derivatives of the embryonic germ layers of endoderm, ectoderm, and mesoderm are involved in tissue formation and organogenesis. What is not yet clear is whether every tissue uses the stem and progenitor model shown to be operative in hematopoiesis (Fig. 3). It is reasonable to propose that most, if not all tissue and organ systems are based on a stem and progenitor model during organogenesis and that stem cells are retained throughout life to participate in regeneration and repair. If this thesis is correct, it would follow that the lessons learned from regeneration and repair of the hematopoietic system might be useful for the regeneration and repair of other organ systems.

The value of using the body's own stem and progenitor cell plan of tissue and organ regeneration is that their numbers and fates are regulated. For example, one cannot deliver too many HSC; regeneration derived from these stem cells results in regulated hematopoiesis. The advantages of a medicine based on stem or progenitor cell transplantation are (i) that one need not understand the process in detail to apply the therapy, (ii) that, the applied therapy should have attendant toxicities only during the acute phase of host preparation for stem or progenitor transplants, and (iii) that the therapy is applied just once. In contrast, medical therapies based on substances that affect endogenous molecular targets will usually have effects and toxicities wherever the molecule is expressed; such therapies are by their nature chronic and are required for the duration of the disease.

Rat neural crest stem cells have also been isolated (41). Using as an assay the clonogenic reconstitution of in vitro multilineage neural cultures, we have enriched for candidate human fetal brain CNS stem

cells (CNS-SCs) (42). The existence of CNS-SCs had been shown by retrovirus marking of cells (43). Transplantation of clonally-marked cells gave rise to neurons and glia whose cell fates were dictated by the regional CNS microenvironment (44). Continuing neurogenesis can occur in the adult brain in particular microenvironments such as the dentate gyrus and the subventricular zone (45). Candidate CNS-SCs at the single-cell level can produce neurospheres of multiple neural cell types; expanded numbers of cells in neurospheres can be prospectively isolated and are clonogenic precursors of neurospheres (42). These neurosphere cells can be transplanted into immunodeficient newborn mice or immunosuppressed adult rats and participate in neurogenesis of neurons and glia.
In skeletal myogenesis, current leading stem cell candidates are the satellite cells (46). Enrichment of precursors for blood vessels (47) and for skin (48) has been accomplished. Several unusual outcomes of cell transplantation have been reported: these include blood derived from clonal neurosphere cultures (49), blood derived from myogenic precursors (likely satellite cells) (50), myogenesis and vasculogenesis from isolated blood and bone marrow precursors (51, 52), and even participation of hematopoietic cells in neurogenesis (53) or liver development (54). It is not clear how this happens. For purposes of this review, the means by which organ-specific stem cells seem to change fate are relevant only to the extent that such cells are potential sources of expanding cells for transplantation (55, 56).

Clinical Transplantation of Stem and Progenitor Cells: Current Practice, Barriers to Their Accomplishments and Opportunities

Hematopoiesis as a model of stem and progenitor transplantation. BM transplantation was invented to enable physicians to increase chemotherapy and radiotherapy to myeloblative doses with the objective of eliminating endogenous cancer cells. The first transplants that were successful were between identical twins, wherein no histocompatibility barrier of host against donor, and no opportunity of immune based reactivity of donor against host, exists (57).
Autologous BM or MPB transplants. Autologous hematopoietic transplants have been used in many patients with cancers, including those of the hematolymphoid system (lymphomas and leukemias), of plasma cells (multiple myeloma), and breast cancer (58). But even if these tumors are sensitive to chemotherapy, only a fraction of patients are cured. Why is this? First, in many patients, disease recurs at the primary site; thus, in many patients the level of therapy did not eliminate endogenous tumor. Second, the bone marrow and the MPB of patients with these cancers are often contaminated with cancer cells (59). Without elimination of these potentially clonogenic cancer cells, it stands to reason that the benefits of high dose chemotherapy could be countermanded by the reintroduction of malignant cells to the circulation. Isolation of human $CD34^{+}Thy^{+}$ HSC from MPB can result in the elimination of detectable malignant multiple myeloma (23, 60), breast cancer (22), and lymphoma cells from the transplant (24). In the trial in Fig. 1C, the number of transplanted malignant cells was undetectable; further clinical trials with human HSC and MPB seem warranted. (I would like to warn the reader that I was co-founder of the company (SyStemix, Inc.) that initiated and carried out the trials, and therefore I might have biases]. It is likely that widespread cures of malignant disease by HSC transplants will not occur unless patients are subscribed earlier in the course of their disease, or if therapies adjuvant to the transplants are attempted. One direction of adjuvant therapy that can eventually be applied will be to attempt to regenerate or reconstitute specific immune responsivity to the small amount of residual tumor. For many tumors, immunity can be induced and is mainly T cell-based. T cell immunity cap detect tumor-unique antigens or tumor-associated peptides that are derived from proteins specific to differentiating cells and are presented on the cell surface by self human lymphocyte antigen (self HLA) molecules (61). The antigen specific T cell receptors that recognize, for example, HLA-A2 and the enclosed melanoma peptide MAGE are entities that retain their specificity no matter whose T cell expresses them, opening the possibility of T cell receptor (TCR) gene transfection to endow antitumor immunity. The collection of T cells that recognize a particular HLA plus tumor peptide can be detected and isolated by a new technology of producing fluorescent major histocompatibility complex, (MHC) peptide tetramers (62). Perhaps TCR transfection. of HSC/CLP/T cells and/or tetramer-based T cell isolation will enable

transplantation of the specific component of immune reconstitution in patients with minimal residual disease following HSC transplant. Additional strategies to augment these immune cell therapies include vaccination with gene-altered tumor cells (63), or augmenting and prolonging the antitumor T cell response by preventing their shutdown (64).

Allogenic Transplantation of Hematopoietic Cells

Allogeneic hematopoietic grafts are potentially useful in cancer treatment, as they are not contaminated with cancer cells; unfortunately, BM and MPB contain T lymphocytes (58, 65). These donor T cells encounter and respond to host antigens in virtually all tissues in the body, leading to a multisystem graft-versus-host (GvH) syndrome (58). HLA-mismatched hematopoietic grafts are usually rejected (66). The high degree of HLA polymorphism makes a random match between unrelated humans a rare event (58). The probability of an HLA match is 25% between siblings. Because MHC molecules process and present any of a number of peptides present within a cell, siblings that share HLA may not share all tissue-specific peptides; these peptides create minor histocompatibility antigens when presented by shared HLA molecules. Minor histocompatibility antigens are important for both host rejection of grafts and GvH immunity (67). HLA-matched host-versus-graft and GvH immunity can largely be controlled by highly immunosuppressive treatments that have attendant risks of chronic immunosuppression (68, 69). Patients given limiting numbers of hematopoietic cells often fail to engraft if T cells are eliminated, but engraft (and get GvH disease) if donor T cells are retained (65). These T cells are said to -"facilitate" engraftment (70-73). The presence of facilitator cells raises the hone that one can cotransplant these cells with HSC to facilitate engraftment without GvH (70-73). However, in mouse models simply raising the HSC dose is sufficient to guarantee rapid and sustained engraftment in the absence of either failure to engraft or GvH, even if the mice are full H-2 mismatches (15, 74). For patients without cancer that require allogeneic hematopoietic or HSC transplants, it would appear that HSC alone at high doses would be most useful. In mouse studies, HSC doses sufficient to obtain rapid engraftment in the autologous setting are also doses sufficient to provide engraftment in the fully allogeneic, MHC mismatched setting (15).

In the case of HLA-matched allotransplants for leukemia, T cells can carry out a graft-versus-leukemia (GvL) response (75). Contained within the population of GvH T cells are cells that can-recognize tissue-specific peptides in the context of shared HLA (76). Clinicians have fine tuned this response to the extent that initial hematopoietic cell grafts can be followed by donor lymphocyte infusions (DLI), when the patient is much healthier and when the patient's GvH response has been controlled. A significant fraction of patients with chronic myelogenous leukemia are in prolonged or complete remission as a result of DLI (77, 78). Recently, "mini-transplants" of HLA-matched MPB into sublethally treated hosts receiving drugs more specific for T cell immunity are followed by DLI; this process provides a lower transplant associated mortality and morbidity, retaining the benefits of GvL (79).

Allogeneic HSC and progenitor transplants can be used in a nonmalignant setting to restore the hematolymphoid system of the host (80). For example, a number of monogenetic disorders lead to deficiencies in cells within the hematolymphoid system, including a variety of severe combined immunodeficiencies and hemoglobin disorders (65). Rep air of the defective enzymes or defective globins could come about either by allogeneic HSC transplants, or autologous gene corrected HSC transplants. The application of transgenic corrections of hematopoietic stem cells has been slowed by problems at a number of stages, but many of these problems have been solved [for example, (81)].

The Use of Allogeneic HSCs for the Induction of Specific Lifelong Transplantation Tolerance

It has been known since the late 1950s that allogeneic bone marrow hematopoietic grafts into irradiated hosts can lead to donor specific chimerism for the life of the host [reviewed in (82)]. These hosts have hematolymphoid systems that are derived wholly or in part from donor stem cells. Such hosts are usually permanently tolerant of donor organ or tissue transplants. Thus, one can transplant fully allogeneic HSC

and cotransplant, for example, hearts from the HSC donors, and produce specific and lifelong acceptance of the transplant, with retention of reactivity to third party grafts and pathogens [reviewed in (80)]. Cotransplantation of HSC and stem cells for other tissues or organs from the. same donor ought to be possible, and ought to enable a circumstance wherein sublethal conditioning of the host permits hematolymphoid chimerism for the purpose of tolerance induction, and cell- and organ-specific regeneration for the replacement of diseased or destroyed organ systems.

Allogeneic HSC Transplants for MHC-Determined Autoimmunity

Many of the autoimmunities are genetically based, especially those that involve an autoimmune response of T cells to organ- or tissue-specific antigens, such as in type I diabetes (the insulin producing islets are their principal target) (83) and multiple sclerosis (the myelinated nerve sheaths are targets). In these cases, the predilection for development of autoimmune T cells can map to particular MHC alleles (84). In mice, HSC transplants from normal donors into lymphoablated diabetogenic (NOD) hosts can abrogate an ongoing diabetogenic autoimmune T cell response (80). The hosts are tolerant of subsequently transplanted donor strain islet grafts (85). Thus, allogeneic HSC transplants can abrogate autoimmunity and induce transplantation tolerance for subsequent stem cell, tissue, or organ grafts.

Transplantation of Nonhematopoietic Stem Celts

The aforementioned models provide a means by which tolerance can be induced to a particular donor set of transplantation antigens. In the case of patients with diseases wherein the generation of mature or maturing cells of a particular organ system is a central problem, cotransplantation of HSCs and nonhematopoietic stem cells should enable organ regeneration.

The recent identification of candidate CNS-SCs and the ability to grow them to large numbers in in vitro cultures should allow testing of the notion that such cells would be capable of regenerating neural or glial elements when necessary (56). Transplantation of tissues that include dopaminergic neurons such as adrenal medulla, fetal ventral mesencephalon, and teratomas are currently being tested in animal models and human cases of Parkinson's disease (45). Rodent CNS cell lines that include CNS-SC, sometimes immortalized with v-myc (86), have been used in a number of models of mouse genetic neurodegenerative diseases, including demyelinating diseases (87), brain gangliosidosis, and other neurodegenerative disorders (88). It is not clear which is the appropriate cell to transplant-the CNS-SCs, the required neurons, or the intermediate progenitors between the two. In the hematopoietic system only HSC are required (11, 15). Although one might think that in the nervous system more differentiated neurons are the appropriate transplants, the normal generation and regeneration of different parts of the brain occurs via stem cells, and it is conceivable that only stem and progenitor cells have both the migratory capacity and the differentiation pathways capable of treatment of these neural defects. Thus, in neurodegenerative diseases, it is important first to determine the rules of transplantation of stem, progenitor, and mature cells, as well as determine the sites into which the transplants must be placed. Other potential neurological disease targets include multiple sclerosis, where an ongoing T cell response might be abrogated by allogeneic HSC transplants or other potent immunosuppressive maneuvers (89). In these cases, remyelination from endogenous precursors is not guaranteed, and the use of neurogenic stem cells, their oligopotent progeny, the immediate precursors of myelinating glia, or the glia cells might provide tissue specific remyelination and regeneration of function. Other potential targets of neural and progenitor cell transplants might include tissues damaged by small strokes, spinal cord injuries, etc.

Transplantation of Other Stem or Progenitor Celts

Liver organ transplants are the therapy of choice in a number of conditions wherein the liver is damaged by toxins, drugs, viral infection, or if the patients have gene defects in the production of important liver-generated factors or receptors. For the most part, liver transplants require a recently deceased but still perfusing donor, and long waiting lists exist for liver transplants. Of course, because donors who

recently died are most likely not HLA-matched to the recipient, liver transplants are usually HLA-disparate and require powerful immunosuppression. It is reasonable to assume that if liver-repopulating stem or progenitor cells are available, sibling transplants may become feasible.
The identification of islet stem and progenitor cell populations appears to be at an earlier phase of development (90). Islet cell transplantation would be preferable to multiple insulin treatments daily, as these are the cells that both. sense the circulating levels of glucose and respond appropriately by releasing insulin at the right dose and tempo. The complications of diabetes are frequent, life shortening, and difficult to manage by insulin therapy. Whole pancreas transplants are difficult, as in liver transplantation. Islet transplants require large numbers of viable cells, and as yet islet cells are difficult to expand in vitro. Thus, it is a reasonable goal to search for conditions wherein islets are continuously generated from stem/progenitor cells, as in some mouse models (90), and to replicate them in vitro.
Muscle regeneration in the case of the intrinsic muscular dystrophies or muscle loss conditions could be life-saving. The recent isolation of skeletal muscle satellite stem cells (46) gives hope that stem cell therapy can be applied to these conditions. Another frequent target for muscle regeneration is the heart, where rapid cell death following coronary artery blockage is a major cause of mortality and morbidity. Unfortunately, the satellite cell equivalent in the heart tissue has not yet been found.
It is reasonable to expect that cotransplantation of HSCs and tissue or organ stem and progenitor cells will occur increasingly over the next two decades and will result from the intersecting advances in stem cell biology and stem/tissue transplant immunology.

BACK HOME

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? s (nerve or neural) and cell and culture and py>1999
          453864  NERVE
          776852  NEURAL
         3697248  CELL
          681293  CULTURE
         2544348  PY>1999
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? t s11/3,ab/all

 11/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13354510   22029638   PMID: 12033726
  Derivation and spontaneous differentiation of human embryonic stem cells.
  Amit Michal; Itskovitz-Eldor Joseph
  Department of Obstetrics and Gynecology, Rambam Medical Center, Haifa,
Israel.
  Journal of anatomy (England)   Mar 2002,  200 (Pt 3)  p225-32,
ISSN 0021-8782   Journal Code: 0137162
  Document type: Journal Article; Review; Review, Tutorial
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: Completed
  Embryonic stem (ES) cells are unique cells derived from the inner
cell mass of the mammalian blastocyst. These cells are immortal and
pluripotent, retain their developmental potential after prolonged
culture , and can be continuously cultured in an undifferentiated
state. Many in vitro differentiation systems have been developed for mouse
ES cells, including reproducible methods for mouse ES cell
 differentiation into haematopoietic and neural precursors,
cardiomyocytes, insulin-secreting cells, endothelial cells and various
other cell types. The derivation of new human ES cell lines
provides the opportunity to develop unique models for developmental
research and for cell therapies. In this review we consider the
derivation and spontaneous differentiation of human ES cells.


 11/3,AB/2     (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13347365   22104493   PMID: 12109143
   Human neural stem and progenitor cells: in vitro and in vivo
properties, and potential for gene therapy and cell replacement in
the CNS.
  Martinez-Serrano A; Rubio F J; Navarro B; Bueno C; Villa A
  Center of Molecular Biology Severo Ochoa, Laboratory CX-450., Autonomous
University of Madrid, Campus Cantoblanco, 28049-Madrid, Spain.
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amserrano@cbm.uam.es
Curr Gene Ther (Netherlands) Sep **2001**, 1 (3) p279-99, ISSN 1566-5232 Journal Code: 101125446
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
The generation of unlimited quantities of **neural** stem and/or progenitor cells derived from the human brain holds great interest for basic and applied neuroscience. In this article we critically **review** the origins and recent developments of procedures developed for the expansion, perpetuation, identification, and isolation of human **neural** precursors, as well as their attributes. Factors influencing their in vitro properties, both under division and after differentiation conditions, are evaluated, with the aim of identifying properties common to the different **culture** systems reported. This analysis suggests that different **culture** procedures result in cells with different properties, or even in different cells being isolated. With respect to in vivo performance, present evidence obtained in rodents indicate that cultured human **neural** precursors, in general, are endowed with excellent integrative properties. Differentiation of the implanted cells, in particular in the case of adult recipients, seems not to be complete, and functionality still needs to be demonstrated. In relation to gene transfer and therapy, aspects currently underexplored, initial data support the view that human **neural** stem and progenitor cells may serve a role as a platform **cell** for the delivery of bioactive substances to the diseased CNS. Although a large deal of basic research remains to be done, available data illustrate the enormous potential that human **neural** precursors isolated, expanded, and characterized in vitro hold for therapeutic applications. In spite of this potential, maintaining a critical view on many unresolved questions will surely help to drive this research field to a good end, that is, the development of real therapies for diseases of the human nervous system.

11/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13199759 22025911 PMID: 12030326
Molecular **cell** biology of Charcot-Marie-Tooth disease.
Berger Philipp; Young Peter; Suter Ueli
Department of Biology, Swiss Federal Institute of Technology, Zurich, Switzerland.
Neurogenetics (England) Mar **2002**, 4 (1) p1-15, ISSN 1364-6745 Journal Code: 9709714
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Charcot-Marie-Tooth disease (CMT), also named hereditary motor and sensory neuropathies, includes a clinically and genetically heterogeneous group of disorders affecting the peripheral nervous system. Traditionally, the different classes of CMT have been divided into demyelinating forms (CMT1, CMT3, and CMT4) and axonal forms (CMT2), a clinically very useful distinction. However, investigations of the underlying molecular and cellular disease mechanisms, mainly accomplished using **cell culture** and animal models, as well as specific re-examination of appropriate patient cohorts, have revealed that the pathological signs of myelinopathies and axonopathies are often intermingled. These findings, although only recently fully appreciated, are not surprising given the dependence and intimate cellular interactions of Schwann cells and neurons, mainly during **nerve** development and, as indicated by the pathology of CMT, also in the adult organism. This **review** is intended to summarize our current knowledge about the molecular and cellular basis of CMT, with a

particular emphasis on the role of Schwann **cell**/axon interactions. Such a view is particularly timely since approximately ten genes have now been identified as culprits in different forms of CMT. This collection revealed novel crucial players in the interplay between Schwann cells and neurons. The analysis of these genes and their encoded proteins will provide additional insights into the molecular and cellular basis of neuropathies and valuable information about the biology and interactions of Schwann cells, their associated neurons, endoneurial fibroblasts, and the **nerve**-surrounding and protecting perineurial sheath.

11/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13105211 21591149 PMID: 11817216
Intracellular, nonreceptor-mediated signaling by adenosine: induction and prevention of neuronal apoptosis.
Wakade A R; Przywara D A; Wakade T D
Department of Pharmacology, School of Medicine, Wayne State University, Detroit, MI 48201, USA. aaade@med.wayne.edu
Molecular neurobiology (United States) Apr-Jun **2001**, 23 (2-3) p137-53, ISSN 0893-7648 Journal Code: 8900963
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Inhibitory effect of adenosine on the isolated heart muscle and vascular system were first described in 1929. Since then, numerous reviews have been published on the diverse actions of this nucleoside on a wide variety of **cell** types. Essentially all effects of adenosine in neurons and non-neuronal cells are mediated by activation of nucleoside membrane receptors coupled to specific intracellular second messenger pathways. This brief **review** describes two novel actions of adenosine in peripheral sympathetic neurons, which are not mediated by adenosine receptors. First is described how adenosine and related nucleosides are able to induce apoptosis during the initial stages of neuronal growth and development in vitro and in vivo. Second is discussed how adenosine is able to prevent or delay apoptosis in more mature sympathetic neurons subjected to **nerve** growth factor deprivation in **culture** . Both the induction and prevention of apoptosis are independent of receptor activation, and totally dependent on the intracellular accumulation and subsequent phosphorylation of adenosine. The physiological significance and mechanisms by which adenosine can induce apoptosis in one situation, and rescue from apoptosis in another, are described in this article.

11/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12902284 21829413 PMID: 11840321
Id and development.
Yokota Y
Department of Biochemistry, Fukui Medical University, Shimoaizuki 23-3, Matsuoka, Fukui 910-1193, Japan. yyokota@fmsrsa.fukui-med.ac.jp
Oncogene (England) Dec 20 **2001**, 20 (58) p8290-8, ISSN 0950-9232 Journal Code: 8711562
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
During development, it is obvious that enormous multiplication and diversification of cells is required to build a body plan from a single fertilized egg and that these two processes, proliferation and differentiation, must be coordinated properly. Id proteins, negative

regulators of basic helix-loop-helix transcription factors, possess the ability to inhibit differentiation and to stimulate proliferation, and are useful molecules for investigating the mechanisms regulating development. In the past few years, our understanding of the roles of Id proteins has been substantially enhanced by the detailed investigation of genetically modified animals. The data have indicated that the functions of Id proteins in vivo are functionally related to those revealed by earlier work in **cell culture** systems. However, unexpected organs and **cell** types have also been found to require Id proteins for their normal development. This **review** looks at the advances made in our understanding of the in vivo functions of Id proteins. The topics discussed include neurogenesis, natural killer **cell** development, lymphoid organogenesis, mammary gland development and spermatogenesis.

11/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12859909 21587159 PMID: 11729753
Large-scale plant micropropagation.
Honda H; Liu C; Kobayashi T
Department of Biotechnology, Graduate School of Engineering, Nagoya University, Nagoya 464-8603, Japan. honda@nubio.nagoya-u.ac.jp
Advances in biochemical engineering/biotechnology (Germany) **2001**, 72 p157-82, ISSN 0724-6145 Journal Code: 8307733
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Plant micropropagation is an efficient method of propagating disease-free, genetically uniform and massive amounts of plants in vitro. The micropropagation from cells can be achieved by direct organogenesis from hairy roots or regeneration via somatic tissue. Once the availability of embryogenic **cell** and hairy root systems based on liquid media has been demonstrated, the scale-up of the whole process should be established by an economically feasible technology for their large-scale production in appropriate bioreactors. It is necessary to design a suitable bioreactor configuration that can provide adequate mixing and mass transfer while minimizing the intensity of shear stress and hydrodynamic pressure. Automatic selection of embryogenic calli and regenerated plantlets using an image analysis procedure should be associated with the system. Using the above systems, it will be possible to establish an advanced plant micropropagation system in which the plantlets can be propagated without soil under optimal conditions controlled in plant factory. The aim of this **review** is to identify the problems related to large-scale plant micropropagation via somatic embryogenesis and hairy roots, and to summarize the most recent developments in bioreactor design. Emphasis is placed on micropropagation technology and computer-aided image analysis, including the successful results obtained in our laboratories.

11/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12768609 21427989 PMID: 11545264
The astrocyte/meningeal **cell** interface--a barrier to successful **nerve** regeneration?
Shearer M C; Fawcett J W
Department of Physiology, University of Cambridge, England. mcs36@cam.ac.uk
Cell and tissue research (Germany) Aug **2001**, 305 (2) p267-73, ISSN 0302-766X Journal Code: 0417625
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed
Following injuries to the adult mammalian CNS meningeal cells migrate into the lesion cavity, forming a fibrotic scar and accessory glia limitans. This infiltration re-establishes the meningeal layer that normally surrounds the CNS, and so reforms the barrier between the CNS and external environment, thus protecting the damaged region from events outside it. However, the newly formed meningeal layer and glia limitans may impede subsequent **nerve** regeneration through the injured region. This structure can be modelled in vitro using an astrocyte/meningeal co-**culture** system. We have examined patterns of neurite outgrowth on such cultures, and we find that axons cross readily from meningeal cells to astrocytes, but are unwilling to cross in the other direction. The distribution of **cell** surface and matrix molecules on these cultures is described, and the effect of various pharmacological interventions which can affect axon growth between the two **cell** types is summarised in this **review**.

11/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12749569 21602179 PMID: 11739603
Protein trafficking mechanisms associated with neurite outgrowth and polarized sorting in neurons.
Tang B L
Central Imaging and Histology Facility and NCA Laboratory, Institute of Molecular and Cell Biology and Department of Biochemistry, National University of Singapore, Republic of Singapore. mcbtbl@imcb.nus.edu.sg
Journal of neurochemistry (United States) Dec **2001**, 79 (5) p923-30, ISSN 0022-3042 Journal Code: 2985190R
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neuronal differentiation in vitro and in vivo involves coordinated changes in the cellular cytoskeleton and protein trafficking processes. I **review** here recent progress in our understanding of the membrane trafficking aspects of neurite outgrowth of neurons in **culture** and selective microtubule-based polarized sorting in fully polarized neurons, focusing on the involvement of some key molecules. Early neurite outgrowth appears to involve the protein trafficking machineries that are responsible for constitutive trans-Golgi network (TGN) to plasma membrane exocytosis, utilizing transport carrier generation mechanisms, SNARE proteins, Rab proteins and tethering mechanisms that are also found in non-neuronal cells. This vectorial TGN-plasma membrane traffic is directed towards several neurites, but can be switch to concentrate on the growth of a single axon. In a mature neuron, polarized targeting to the specific axonal and dendritic domains appears to involve selective microtubule-based mechanisms, utilizing motor proteins capable of distinguishing microtubule tracks to different destinations. The apparent gaps in our knowledge of these related protein transport processes will be highlighted.

11/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12558916 21462387 PMID: 11578751
The molecular bases of Alzheimer's disease and other neurodegenerative disorders.
Maccioni R B; Munoz J P; Barbeito L
Millennium Institute for Advanced Studies in Cell Biology and Biotechnology, Faculty of Sciences, University of Chile, Santiago, Chile. rmaccion@uchile.cl

Archives of medical research (United States) Sep-Oct **2001**, 32 (5) p367-81, ISSN 0188-4409 Journal Code: 9312706
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Alzheimer's disease, the cause of one of the most common types of dementia, is a brain disorder affecting the elderly and is characterized by the formation of two main protein aggregates: senile plaques and neurofibrillary tangles, which are involved in the process leading to progressive neuronal degeneration and death. Neurodegeneration in Alzheimer's disease is a pathologic condition of cells rather than an accelerated way of aging. The senile plaques are generated by a deposition in the human brain of fibrils of the beta-amyloid peptide (Abeta), a fragment derived from the proteolytic processing of the amyloid precursor protein (APP). Tau protein is the major component of paired helical filaments (PHFs), which form a compact filamentous network described as neurofibrillary tangles (NFTs). Experiments with hippocampal cells in **culture** have indicated a relationship between fibrillary amyloid and the cascade of molecular signals that trigger tau hyperphosphorylations. Two main protein kinases have been shown to be involved in anomalous tau phosphorylations: the cyclin-dependent kinase Cdk5 and glycogen synthase kinase GSK3beta. Cdk5 plays a critical role in brain development and is associated with neurogenesis as revealed by studies in brain cells in **culture** and neuroblastoma cells. Deregulation of this protein kinase as induced by extracellular amyloid loading results in tau hyperphosphorylations, thus triggering a sequence of molecular events that lead to neuronal degeneration. Inhibitors of Cdk5 and GSK3beta and antisense oligonucleotides exert protection against neuronal death. On the other hand, there is cumulative evidence from studies in cultured brain cells and on brains that oxidative stress constitutes a main factor in the modification of normal signaling pathways in neuronal cells, leading to biochemical and structural abnormalities and neurodegeneration as related to the pathogenesis of Alzheimer's disease. This **review** is focused on the main protein aggregates responsible for neuronal death in both sporadic and familial forms of Alzheimer's disease, as well as on the alterations in the normal signaling pathways of functional neurons directly involved in neurodegeneration. The analysis is extended to the action of neuroprotective factors including selective inhibitors of tau phosphorylating protein kinases, estrogens, and antioxidants among other molecules that apparently prevent neuronal degeneration.

11/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11254792 21289951 PMID: 11395921
Mesenchymal stem cells.
Minguell J J; Erices A; Conget P
Unidad de Biologia Celular, INTA, Universidad de Chile, Casilla 138, Santiago 11, Chile. jminguel@uec.inta.uchile.cl
Experimental biology and medicine (Maywood, N.J.) (United States) Jun **2001**, 226 (6) p507-20, ISSN 1535-3702 Journal Code: 100973463
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Within the bone marrow stroma there exists a subset of nonhematopoietic cells referred to as mesenchymal stem or mesenchymal progenitor cells. These cells can be ex vivo expanded and induced, either in vitro or in vivo, to terminally differentiate into osteoblasts, chondrocytes, adipocytes, tenocytes, myotubes, **neural** cells, and hematopoietic-supporting stroma. The multipotential of these cells, their easy isolation and **culture**, as well as their high ex vivo expansive

potential make these cells an attractive therapeutic tool. In this work we will **review** the information dealing with the biology of mesenchymal progenitors as it has been revealed mainly by ex vivo studies performed with bone marrow-derived cells. The discussed topics include, among others, characteristics of mesenchymal progenitors, evidence for the existence of a vast repertoire of uncommitted and committed progenitors both in the bone marrow and in mesenchymal tissues, a diagram for their proliferative hierarchy, and comments on mobilization, microenvironment, and clinical use of mesenchymal progenitors. Despite the enormous data available at molecular and cellular levels, it is evident that a number of fundamental questions still need to be resolved before mesenchymal progenitors can be used for safe and effective clinical applications in the context of both **cell** and gene therapies.

11/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11020754 21014487 PMID: 11131546
Cell replacement strategies for neurodegenerative disorders.
Bjorklund A
Wallenberg Neuroscience Center, Department of Physiological Sciences, Lund University, Solvegatan 17, S-223 62 Lund, Sweden.
Novartis Foundation symposium (England) **2000**, 231 p7-15; discussion 16-20, Journal Code: 9807767
Document type: Journal Article; Review; Review Literature
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cell transplantation has over the last two decades emerged as a promising approach for restoration of function in neurodegenerative diseases, in particular Parkinson's and Huntington's disease. Clinical trials have so far focused on the use of implants of embryonic mesencephalic tissue containing already fate-committed dopaminergic neuroblasts with the capacity to develop into fully mature dopamine neurons in their new location in the host brain. However, the recent demonstration that immature **neural** progenitor cells with multipotent properties can be isolated from both the developing and adult CNS and that these cells can be maintained and propagated in **culture** , has provided a new interesting tool for restorative **cell** replacement and gene transfer therapies. Embryonic stem cells, obtained from the early stages of embryonic development, and **neural** stem cells, obtained from the developing brain, may provide renewable sources of cells for therapeutic purposes, and could eventually offer a powerful alternative to primary fetal CNS tissue in clinical transplantation protocols. The purpose of this **review** is to discuss the prospects of the emerging progenitor **cell** technology for **cell** replacement and restorative therapies in neurodegenerative diseases, and consider some of the critical issues that must be solved in order to make progenitor cells useful in studies of brain repair.

11/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10811752 20351308 PMID: 10891876
Neurotrophins and development of the rod pathway: an elementary deduction.
Rickman D W
Department of Ophthalmology and Visual Sciences, University of Iowa College of Medicine, Iowa City, Iowa. rickm004@mc.duke.edu
Microscopy research and technique (UNITED STATES) Jul 15 **2000**, 50 (2) p124-9, ISSN 1059-910X Journal Code: 9203012
Contract/Grant No.: EY11389; EY; NEI

Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The rodent retina is a particularly attractive model for the study of neuronal developmental processes since considerable neurogenesis, cellular migration, phenotypic differentiation of retinal **cell** types and synaptogenesis occurs postnatally. In addition, the retina is readily accessible to surgical intervention, pharmacological manipulation, and local suppression of gene expression-tools that can be utilized to study mechanisms underlying the development of retinal neurons and their interconnections that form distinct functional circuits. Here, I **review** our studies describing the ontogeny of a specific retinal interneuron, the AII amacrine **cell**, an integral element in the rod (scotopic) pathway. Specifically, we used a number of approaches to examine the potential role of neurotrophic factors on the morphological and neurochemical differentiation of the AII. Copyright 2000 Wiley-Liss, Inc.

11/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10797944 20342278 PMID: 10880854
Metabolism and functions of glutathione in brain.
Dringen R
Physiologisch-chemisches Institut der Universitat, Hoppe-Seyler-Str. 4, D-72076 Tubingen, Germany. ralf.dringen@uni-tuebingen.de
Progress in neurobiology (ENGLAND) Dec **2000**, 62 (6) p649-71, ISSN 0301-0082 Journal Code: 0370121
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The tripeptide glutathione is the thiol compound present in the highest concentration in cells of all organs. Glutathione has many physiological functions including its involvement in the defense against reactive oxygen species. The cells of the human brain consume about 20% of the oxygen utilized by the body but constitute only 2% of the body weight. Consequently, reactive oxygen species which are continuously generated during oxidative metabolism will be generated in high rates within the brain. Therefore, the detoxification of reactive oxygen species is an essential task within the brain and the involvement of the antioxidant glutathione in such processes is very important. The main focus of this **review** article will be recent results on glutathione metabolism of different brain **cell** types in **culture**. The glutathione content of brain cells depends strongly on the availability of precursors for glutathione. Different types of brain cells prefer different extracellular glutathione precursors. Glutathione is involved in the disposal of peroxides by brain cells and in the protection against reactive oxygen species. In coculture astroglial cells protect other **neural cell** types against the toxicity of various compounds. One mechanism for this interaction is the supply by astroglial cells of glutathione precursors to neighboring cells. Recent results confirm the prominent role of astrocytes in glutathione metabolism and the defense against reactive oxygen species in brain. These results also suggest an involvement of a compromised astroglial glutathione system in the oxidative stress reported for neurological disorders.

11/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10625604 20161496 PMID: 10696506
Inflammatory mediators and modulation of blood-brain barrier

permeability.

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Cellular and molecular neurobiology (UNITED STATES) Apr **2000**, 20 (2) p131-47, ISSN 0272-4340 Journal Code: 8200709
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

1. Unlike some interfaces between the blood and the nervous system (e.g., **nerve** perineurium), the brain endothelium forming the blood-brain barrier can be modulated by a range of inflammatory mediators. The mechanisms underlying this modulation are reviewed, and the implications for therapy of the brain discussed. 2. Methods for measuring blood-brain barrier permeability in situ include the use of radiolabeled tracers in parenchymal vessels and measurements of transendothelial resistance and rate of loss of fluorescent dye in single pial microvessels. In vitro studies on **culture** models provide details of the signal transduction mechanisms involved. 3. Routes for penetration of polar solutes across the brain endothelium include the paracellular tight junctional pathway (usually very tight) and vesicular mechanisms. Inflammatory mediators have been reported to influence both pathways, but the clearest evidence is for modulation of tight junctions. 4. In addition to the brain endothelium, **cell** types involved in inflammatory reactions include several closely associated cells including pericytes, astrocytes, smooth muscle, microglia, mast cells, and neurons. In situ it is often difficult to identify the site of action of a vasoactive agent. In vitro models of brain endothelium are experimentally simpler but may also lack important features generated in situ by **cell:cell** interaction (e.g. induction, signaling). 5. Many inflammatory agents increase both endothelial permeability and vessel diameter, together contributing to significant leak across the blood-brain barrier and cerebral edema. This **review** concentrates on changes in endothelial permeability by focusing on studies in which changes in vessel diameter are minimized. 6. Bradykinin (Bk) increases blood-brain barrier permeability by acting on B2 receptors. The downstream events reported include elevation of [Ca2+]i, activation of phospholipase A2, release of arachidonic acid, and production of free radicals, with evidence that IL-1 beta potentiates the actions of Bk in ischemia. 7. Serotonin (5HT) has been reported to increase blood-brain barrier permeability in some but not all studies. Where barrier opening was seen, there was evidence for activation of 5-HT2 receptors and a calcium-dependent permeability increase. 8. Histamine is one of the few central nervous system neurotransmitters found to cause consistent blood-brain barrier opening. The earlier literature was unclear, but studies of pial vessels and cultured endothelium reveal increased permeability mediated by H2 receptors and elevation of [Ca2+]i and an H1 receptor-mediated reduction in permeability coupled to an elevation of cAMP. 9. Brain endothelial cells express nucleotide receptors for ATP, UTP, and ADP, with activation causing increased blood-brain barrier permeability. The effects are mediated predominantly via a P2U (P2Y2) G-protein-coupled receptor causing an elevation of [Ca2+]i; a P2Y1 receptor acting via inhibition of adenyl cyclase has been reported in some in vitro preparations. 10. Arachidonic acid is elevated in some **neural** pathologies and causes gross opening of the blood-brain barrier to large molecules including proteins. There is evidence that arachidonic acid acts via generation of free radicals in the course of its metabolism by cyclooxygenase and lipoxygenase pathways. 11. The mechanisms described reveal a range of interrelated pathways by which influences from the brain side or the blood side can modulate blood-brain barrier permeability. Knowledge of the mechanisms is already being exploited for deliberate opening of the blood-brain barrier for drug delivery to the brain, and the pathways capable of reducing permeability hold promise for therapeutic treatment of inflammation and cerebral edema.

11/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10512231 20060111 PMID: 10592526
Electronic noses for bioreactor monitoring.
Mandenius C F
Department of Physics and Measurement Technology, Linkoping University, Sweden. cfm@ifm.liu.se
Advances in biochemical engineering/biotechnology (GERMANY) **2000**, 66 p65-82, ISSN 0724-6145 Journal Code: 8307733
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Electronic noses provide new possibilities for monitor the state of a cultivation non-invasively in real-time. The electronic nose uses an array of chemical gas sensors that monitors the off-gas from the bioreactor. By taking advantage of the off-gas components' different affinities towards the sensors in the array it is possible with the help of pattern recognition methods to extract valuable information from the **culture** in a way similar to the human nose. For example, with artificial **neural** networks, metabolite and biomass concentration can be predicted, the fermentability of a medium before starting the fermentation estimated, and the growth and production stages of the **culture** visualized. In this **review** these and other recent results with electronic noses from monitoring microbial and **cell** cultures in bioreactors are described.

11/3,AB/16 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13755640 BIOSIS NO.: 200200384461
Developmental potential of hematopoietic and **neural** stem cells: Unique or all the same?
AUTHOR: Kirchhof Nicole; Harder Friedrich; Petrovic Suzana; Kreutzfeldt Simon; Schmittwolf Carolin; Duerr Michael; Kirsten Jan; Muehl Bettina; Merkel Angela; Mueller Albrecht M(a)
AUTHOR ADDRESS: (a)Institut fuer Medizinische Strahlenkunde und Zellforschung (MSZ), Universitaet Wuerzburg, Versbacherstrasse 5, D-97078, Wuerzburg**Germany E-Mail: albrecht.mueller@mail.uni-wuerzburg.de
JOURNAL: Cells Tissues Organs 171 (1):p77-89 **2002**
MEDIUM: print
ISSN: 1422-6405
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Like many other animals, mammals develop from fertilized oocytes-the ultimate stem cells. As embryogenesis proceeds, most cells lose developmental potential and eventually become restricted to a specific **cell** lineage. The result is the formation of a complete and structured mature organism with complex organs composed of a great variety of mature, mostly mitotically quiescent effector cells. However, along the way, some exceptional cells, known as somatic stem cells (SSCs) are set aside and maintain a high proliferation and tissue-specific differentiation potential. SSCs, in contrast to embryonic stem (ES) cells, which are able to give rise to all **cell** types of the body, have been regarded as being more limited in their differentiation potential in the sense that they were thought to be committed exclusively to their tissue of origin. However, recent studies have demonstrated that

somatic stem cells from a given tissue can also contribute to heterologous tissues and thus show a broad non-tissue restricted differentiation potential. The question arises: how plastic are somatic stem cells? To provide a tentative answer, we describe and **review** here recent investigations into the developmental potentials of two somatic stem **cell** types, namely hematopoietic and **neural** stem cells.

2002

11/3,AB/17 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13515652 BIOSIS NO.: 200200144473
Chemokines and Alzheimer's disease.
AUTHOR: Streit Wolfgang J(a); Conde Jessica R; Harrison Jeffrey K
AUTHOR ADDRESS: (a)Department of Neuroscience, University of Florida College of Medicine and McKnight Brain Institute, Gainesville, FL, 32611 **USA E-Mail: streit@ufbi.ufl.edu
JOURNAL: Neurobiology of Aging 22 (6):p909-913 November-December, **2001**
MEDIUM: print
ISSN: 0197-4580
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In recent years, increasing attention has been focused on chemokines as inflammatory mediators in the CNS. The limited number of studies that have investigated chemokine and chemokine receptor expression in Alzheimer's disease (AD) brain and in **cell culture** models seem to support a role for inflammation in AD pathogenesis. Here we provide a **review** of these studies, but in addition, point out the possible role of chemokines as communication molecules between neurons and microglia. Understanding neuron-microglia interactions is essential for understanding AD pathogenesis, and disturbances in chemokine-mediated intercellular communication may contribute toward a generalized impairment of microglial **cell** function.

2001

11/3,AB/18 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13489624 BIOSIS NO.: 200200118445
Chemosensitivity of serotonergic neurons in the rostral ventral medulla.
AUTHOR: Richèrson George B(a); Wang Wengang; Tiwari Jyoti; Bradley Stefania Risso
AUTHOR ADDRESS: (a)Department of Neurology, Yale University School of Medicine, 15 York St, New Haven, CT, 06520-8018**USA E-Mail: george.richerson@yale.edu
JOURNAL: Respiration Physiology 129 (1-2):p175-189 December, **2001**
MEDIUM: print
ISSN: 0034-5687
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The medullary raphe contains two subtypes of chemosensitive

neuron: one that is stimulated by acidosis and another that is inhibited. Both types of neuron are putative chemoreceptors, proposed to act in opposite ways to modulate respiratory output and other pH sensitive brain functions. In this **review**, we will discuss the cellular properties of these chemosensitive raphe neurons when studied in vitro using brain slices and primary dissociated **cell culture**. Quantification of chemosensitivity of raphe neurons indicates that they are highly sensitive to small changes in extracellular pH (pHo) between 7.2 and 7.6. Stimulation by acidosis occurs only in the specific phenotypic subset of neurons within the raphe that are serotonergic. These serotonergic neurons also have other properties consistent with a specialized role in chemoreception. Homologous serotonergic neurons are present within the ventrolateral medulla (VLM), and may have contributed to localization of respiratory chemoreception to that region. Chemosensitivity of raphe neurons increases in the postnatal period in rats, in parallel with development of respiratory chemoreception in vivo. An abnormality of serotonergic neurons of the ventral medulla has been identified in victims of sudden infant death syndrome (SIDS). The cellular properties of serotonergic raphe neurons suggest that they play a role in the CNS response to hypercapnia, and that they may contribute to interactions between the sleep/wake cycle and respiratory control.

2001

11/3,AB/19 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13359570 BIOSIS NO.: 200100566719
Mechanisms of action of docosahexaenoic acid in the nervous system.
AUTHOR: Salem Norman Jr(a); Litman Burton; Kim Hee-Yong; Gawrisch Klaus
AUTHOR ADDRESS: (a)12420 Parklawn Dr., Room 150, Rockville, MD, 20852: nsalem@dicbr.niaaa.nih.gov**USA
JOURNAL: Lipids 36 (9):p945-959 September, **2001**
MEDIUM: print
ISSN: 0024-4201
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: This **review** describes (from both the animal and human literature) the biological consequences of losses in nervous system docosahexaenoate (DHA). It then concentrates on biological mechanisms that may serve to explain changes in brain and retinal function. Brief consideration is given to actions of DHA as a nonesterified fatty acid and as a docosanoid or other bioactive molecule. The role of DHA-phospholipids in regulating G-protein signaling is presented in the context of studies with rhodopsin. It is clear that the visual pigment responds to the degree of unsaturation of the membrane lipids. At the **cell** biological level, DHA is shown to have a protective role in a **cell culture** model of apoptosis in relation to its effects in increasing cellular phosphatidylserine (PS); also, the loss of DHA leads to a loss in PS. Thus, through its effects on PS, DHA may play an important role in the regulation of **cell** signaling and in **cell** proliferation. Finally, progress has been made recently in nuclear magnetic resonance studies to delineate differences in molecular structure and order in biomembranes due to subtle changes in the degree of phospholipid unsaturation.

2001

11/3,AB/20 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13355782 BIOSIS NO.: 200100562931
Regulation of corpora allata in females of Pyrrhocoris apterus (Heteroptera) (A mini-**review**).
AUTHOR: Hodkova M(a); Okuda T; Wagner R M
AUTHOR ADDRESS: (a)Institute of Entomology, Czech Academy of Sciences, Branisovska 31, 370 05, Ceske Budejovice: magda@entu.cas.cz**Czech Republic
JOURNAL: In Vitro Cellular & Developmental Biology Animal 37 (9):p560-563 October, **2001**
MEDIUM: print
ISSN: 1071-2690
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Mechanisms for the transduction of photoperiodic and food signals to the corpus allatum (CA) are described. The focus of this paper is on the control of the CA by the brain in adult females of the firebug, Pyrrhocoris apterus. By using surgical interventions to the neuroendocrine complex of brain-subesophageal ganglion-corpora cardiaca-CA (BR-SG-CC-CA) in vivo and in vitro we were able to identify two regulatory pathways. (1) Slow regulation of the CA activity (stimulation or inhibition) needs a relatively long period of time to be accomplished (several d) in vivo and is associated with changes of the gland **cell** volume and ultrastructure. The stimulated or inhibited activity of the CA is maintained during short-term incubation of the isolated CA in vitro. (2) Fast inhibition of the CA activity is reversible during short-term incubation in vitro; the CA can be switched from lower to higher activity and vice versa, depending on the presence or absence of the BR-SG in the medium. Both slow and fast regulatory factors originate in the pars intercerebralis of the brain and in intact neuroendocrine complex they reach the CA via nerves. A slow inhibitor, induced by short d, causes reproductive diapause. A fast inhibitor prevents ovarian maturation in starved nondiapausing females. A slow stimulator, induced by feeding under long d, overcomes the fast inhibition of the CA, thereby stimulating vitellogenesis. Food signals are transmitted to the brain via humoral pathways.

2001

11/3,AB/21 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13319581 BIOSIS NO.: 200100526730
Versatile stem cells, young and old. A **review**.
AUTHOR: Eridani Sandro(a)
AUTHOR ADDRESS: (a)Institute of Advanced Biomedical Technology, ITBA, National Research Council, Milano: eridani@itba.mi.cnr.it**Italy
JOURNAL: Cytotechnology 35 (2):p137-143 **2001**
MEDIUM: print
ISSN: 0920-9069
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Both embryonic and somatic stem cells have been studied in recent

years with particular regard to their differentiation potential. In vitro studies allow a considerable amplification of such cells in **culture** as well as the induction of commitment in different directions under proper stimulating factors. Moreover, a surprising versatility has been discovered, which makes possible a 'reprogramming' of stem cells into a lineage pathway which may be completely different from the expected direction: for instance, a production of brain cells from blood progenitors has been obtained. It is thus possible to envisage methods of producing in **culture** sufficient amounts of stem cells, committed to a certain pathway, which can be transplanted in vivo to replace damaged tissues and organs.

2001

11/3,AB/22 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13240614 BIOSIS NO.: 200100447763
Caspase inhibition: A potential therapeutic strategy in neurological diseases.
AUTHOR: Rideout H J; Stefanis L(a)
AUTHOR ADDRESS: (a)Department of Neurology, Columbia University, 650 West 168th Street, Black Building Rm No. 326, New York, NY, 10032: LS76@columbia.edu**USA
JOURNAL: Histology and Histopathology 16 (3):p895-908 July, **2001**
MEDIUM: print
ISSN: 0213-3911
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Caspases are intracellular proteases that participate in apoptotic pathways in mammalian cells, including neurons. Here we **review** evidence that caspase inhibition, through pharmacological or molecular means, may inhibit neuronal **cell** death in a number of in vitro and in vivo models of neurological disease. It has recently become clear that, at least in most **cell culture** models, caspase inhibition offers only transient protection, and that a caspase-independent death eventually occurs. This may be due to irreversible caspase-independent alterations at the level of the mitochondria. Despite concerns that targeting caspases alone may prove insufficient to truly reverse the effects of various death stimuli, in vivo studies indicate that caspase inhibition promotes survival and functional outcome in a variety of neurological disease models. In addition, studies of human post-mortem material suggest that caspases are activated in certain human neurological diseases. Caspase inhibition may therefore provide a novel strategy for the treatment of such disorders. Caspases, through the generation of toxic fragments of critical protein substrates, may also be involved in earlier steps of neuronal dysfunction, such as protein aggregation in Huntington's and Alzheimer's disease, and therefore caspase inhibition may be of additional value in the treatment of these particular disorders.

2001

11/3,AB/23 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13122390 BIOSIS NO.: 200100329539

Neural activity and survival in the developing nervous system.
AUTHOR: Mennerick Steven; Zorumski Charles F(a)
AUTHOR ADDRESS: (a)Department of Psychiatry, and Department of Anatomy and Neurobiology, Washington University School of Medicine, 660 S. Euclid Ave., Saint Louis, MO, 63110: zorumskc@psychiatry.wustl.edu**USA
JOURNAL: Molecular Neurobiology 22 (1-3):p41-54 August-October-December, **2000**
MEDIUM: print
ISSN: 0893-7648
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recent evidence suggests that blockade of normal excitation in the immature nervous system may have profound effects on neuronal survival during the period of natural **cell** death. **Cell** loss following depression of electrical activity in the central nervous system (CNS) may explain the neuropsychiatric deficits in humans exposed to alcohol or other CNS depressants during development. Thus, understanding the role of electrical activity in the survival of young neurons is an important goal of modern basic and clinical neuroscience. Here we **review** the evidence from in vivo and in vitro model systems that electrical activity participates in promoting neuronal survival. We discuss the potential role of moderate elevations of intracellular calcium in promoting survival, and we address the possible ways in which activity and conventional trophic factors may interact.

2000

11/3,AB/24 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13115585 BIOSIS NO.: 200100322734
Positive stealth virus cultures in myeloma patients: A possible explanation for neuropsychiatric co-morbidity.
AUTHOR: Durie Brian G M(a); Collins Russell A; Martin W John
AUTHOR ADDRESS: (a)Cancer Center, Cedars Sinai Medical Center, Los Angeles, CA**USA
JOURNAL: Blood 96 (11 Part 1):p360a November 16, **2000**
MEDIUM: print
CONFERENCE/MEETING: 42nd Annual Meeting of the American Society of Hematology San Francisco, California, USA December 01-05, 2000
SPONSOR: American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We have used viral **culture** techniques to screen patients with multiple myeloma for the presence of stealth-adapted viruses: a newly defined grouping of atypically-structured, poorly immunogenic viruses which induce a characteristic vacuolating cytopathic effect (CPE) in human and animal **cell** lines. Electron microscopy, serology and molecular-based assays have been used to further differentiate stealth-adapted viruses from conventional cytopathic viruses. Peripheral blood mononuclear cells from 20 patients with multiple myeloma were added to human MRC-5 fibroblasts. All cultures showed unequivocal, extensive foamy syncytial **cell** formation. Mononuclear cells from 10 patients were re-tested in a blinded fashion along with 10 samples obtained randomly from hospital outpatients. Nine of the 10 myeloma patient samples rapidly gave strong positives; the 10th became positive with

serial observation, whereas no (zero) controls became positive. Positive cultures have also been obtained from bone marrow, CSF and pleural fluid of myeloma patients. Stealth viral infections have previously been linked to encephalopathy with complex and diverse neuropsychiatric manifestations. Detailed clinical **review** of the tested myeloma patients revealed neurologic abnormalities in 4 patients (brain and meningeal plamacytomata, facial myoclonic seizures and **nerve** deafness), and prior neuropsychiatric abnormalities in a further 9 patients (ranging from emotional/cognitive difficulties to chronic fatigue syndrome). Since stealth virus replication can lead to varying re-combinations of mutated viral and cellular genetic sequences, virus assimilation and over-expression of genes coding myeloma growth factors could enable a stealth-adapted virus to promote the development of myeloma. Assessment of this will require sequence comparisons of stealth viruses from patients with and without myeloma. Our observations warrant these and other studies to clarify the significance of positive stealth virus cultures in myeloma patients.

2000

11/3,AB/25 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13089063 BIOSIS NO.: 200100296212
Reconstructing smell.
AUTHOR: Barber Robert D; Ronnett Gabriele V(a)
AUTHOR ADDRESS: (a)Department of Neuroscience, Johns Hopkins University School of Medicine, 725 North Wolfe Street, Baltimore, MD, 21205: gronnett@jhmi.edu**USA
JOURNAL: Molecular Neurobiology 21 (3):p161-173 June, **2000**
MEDIUM: print
ISSN: 0893-7648
DOCUMENT TYPE: Article; Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Odorant signal transduction and neurogenesis are fundamental properties of the olfactory epithelium. Many preparations have been used to elucidate some of the mechanisms underlying these properties. In this article, we briefly **review** these research areas and describe some of the techniques used to obtain the data. We focus specifically on the **cell-culture** paradigm and the data obtained from various immortal **cell** lines in their attempts to reconstruct the olfactory epithelium in vitro.

2000

11/3,AB/26 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13077098 BIOSIS NO.: 200100284247
Neuronal **cell** death in nervous system development, disease, and injury (**review**).
AUTHOR: Martin Lee J(a)
AUTHOR ADDRESS: (a)Department of Pathology, Johns Hopkins University School of Medicine, 720 Rutland Avenue, 558 Ross Building, Baltimore, MD, 21205-2196: lmartin@jhmi.edu**USA
JOURNAL: International Journal of Molecular Medicine 7 (5):p455-478 May, **2001**

MEDIUM: print
ISSN: 1107-3756
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Neuronal death is normal during nervous system development but is abnormal in brain and spinal cord disease and injury. Apoptosis and necrosis are types of **cell** death. They are generally considered to be distinct forms of **cell** death. The re-emergence of apoptosis may contribute to the neuronal degeneration in chronic neurodegenerative disease, such as amyotrophic lateral sclerosis and Alzheimer's disease, and in neurological injury such as cerebral ischemia and trauma. There is also mounting evidence supporting an apoptosis-necrosis **cell** death continuum. In this continuum, neuronal death can result from varying contributions of coexisting apoptotic and necrotic mechanisms; thus, some of the distinctions between apoptosis and necrosis are becoming blurred. **Cell culture** and animal model systems are revealing the mechanisms of **cell** death. Necrosis can result from acute oxidative stress. Apoptosis can be induced by **cell** surface receptor engagement, growth factor withdrawal, and DNA damage. Several families of proteins and specific biochemical signal-transduction pathways regulate **cell** death. **Cell** death signaling can involve plasma membrane death receptors, mitochondrial death proteins, proteases, kinases, and transcription factors. Players in the **cell** death and **cell** survival orchestra include Fas receptor, Bcl-2 and Bax (and their homologues), cytochrome c, caspases, p53, and extracellular signal-regulated protein kinases. Some forms of **cell** death require gene activation, RNA synthesis, and protein synthesis, whereas others forms are transcriptionally-translationally-independent and are driven by posttranslational mechanisms such as protein phosphorylation and protein translocation. A better understanding of the molecular mechanisms of neuronal **cell** death in nervous system development, injury and disease can lead to new therapeutic approaches for the prevention of neurodegeneration and neurological disabilities and will expand the field of **cell** death biology.

2001

11/3,AB/27 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12938950 BIOSIS NO.: 200100146099
In vivo imaging of the mammalian nervous system using fluorescent proteins.
AUTHOR: Tucker Kerry Lee(a)
AUTHOR ADDRESS: (a)Department of Neurobiochemistry, Max Planck Institute of Neurobiology, Am Klopferspitz 18a, 82152, Martinsried: klt@fmi.ch** Germany
JOURNAL: Histochemistry and Cell Biology 115 (1):p31-39 January,
2001
MEDIUM: print
ISSN: 0948-6143
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The recent development of fluorescent proteins has rapidly and radically altered the way **cell** biology is performed by allowing simple, non-invasive imaging of cellular processes in real time. The special properties of the nervous system, such as synaptic morphology,

axonal/dendritic maturation, and neuronal migration are especially amenable to investigation using fluorescent proteins. This **review** focuses on the various genetic and viral vectors used to express fluorescent proteins in vivo and in slice **culture**, and the strengths and limitations associated with them.

2001

11/3,AB/28 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12928191 BIOSIS NO.: 200100135340
In vitro **cell** systems in prions investigation (**review**).
AUTHOR: Dagdanova A V; D'yakonov L P
JOURNAL: Sel'skokhozyaistvennaya Biologiya (6):p3-10 November-December, **2000**
MEDIUM: print
ISSN: 0131-6397
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Russian; Non-English
SUMMARY LANGUAGE: English; Russian

ABSTRACT: The recent data of prions investigation with use of **cell culture** were presented. The mechanism of programme of **cell** death - apoptosis of neurones, which is induced by prions, was described. As a result of experiments the **cell** cultures infected by scrapie agent were obtained. The ability of use of the **cell** cultures as models for investigation and diagnosis of the diseases caused by prions was discussed.

2000

11/3,AB/29 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12814285 BIOSIS NO.: 200100021434
How does interleukin 15 contribute to the pathogenesis of HTLV type 1-associated myelopathy/tropical spastic paraparesis?
AUTHOR: Azimi Nazli(a); Mariner Jennifer; Jacobson Steven; Waldmann Thomas A
AUTHOR ADDRESS: (a)National Cancer Institute, National Institutes of Health, 10 Center Drive, Building 10, Room 4N-102, MSC 1274, Bethesda, MD, 20892-1374: nazli@helix.nih.gov**USA
JOURNAL: AIDS Research and Human Retroviruses 16 (16):p1717-1722 November 1, **2000**
MEDIUM: print
ISSN: 0889-2229
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: HTLV-1 is the etiological agent of a neurological disease named HAM/TSP that has clinical characteristics similar to those of multiple sclerosis (MS). The PBMC obtained from HAM/TSP patients undergo spontaneous proliferation in the absence of addition of any exogenous cytokines in an ex vivo **culture**. This spontaneous proliferation has been thought to be due to the proliferation of T cells. It was demonstrated that this proliferation is, in part, due to the production

of IL-2 and its receptor (IL-2Ralpha) by HTLV-1-infected T cells. In this **review**, we demonstrate that IL-15 production also contributes to the spontaneous proliferation of T cells obtained from HAM/TSP PBMC. We provide data indicating that IL-15 expression is elevated in HAM/TSP PBMC when compared to that of the normal donors. Furthermore, we demonstrate that IL-15 overexpression by HTLV-1 is due to Tax trans-activation of its promoter and induction of NF-kappaB transcription factors. On the basis of these studies, we propose a model in which HTLV-1 infection of T cells results in the production of both IL-2 and IL-15 cytokines, growth factors that support the proliferation of T cells.

2000

11/3,AB/30 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12720046 BIOSIS NO.: 200000473548
Motor neuron disease in vitro: The use of cultured motor neurons to study amyotrophic lateral sclerosis.
AUTHOR: Bar P R(a)
AUTHOR ADDRESS: (a)Laboratory for Experimental Neurology, Rudolf Magnus Institute for Neurosciences, University Medical Centre, Utrecht, 3508 GA, Utrecht**Netherlands
JOURNAL: European Journal of Pharmacology 405 (1-3):p285-295 29 September, **2000**
MEDIUM: print
ISSN: 0014-2999
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Amyotrophic lateral sclerosis (ALS) is a lethal neurodegenerative disease in which motor neurons in the nervous system die. The cause is unknown, and no effective treatment exists. Mutations in the gene for superoxide dismutase found in a subpopulation have led to an animal model, but research with these mice has not produced complete insight into the disease mechanism. Studies with isolated motor neurons may produce important information. This **review** discusses approaches to **culture** motor neurons - single cells, cocultured with other cells, and in intact preparations, such as the spinal or cortical slice. Motor neurons in monoculture are suitable for acute but not for chronic studies, whereas cocultures and slices survive up to months and are used for chronic studies. Results with toxic substances believed to play a role in the disease, such as oxidants and glutamate, and of studies where the energy status of the cells is manipulated, are presented.

2000

11/3,AB/31 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12644242 BIOSIS NO.: 200000397744
Glutathione metabolism in brain: Metabolic interaction between astrocytes and neurons in the defense against reactive oxygen species.
AUTHOR: Dringen Ralf(a); Gutterer Jan M; Hirrlinger Johannes
AUTHOR ADDRESS: (a)Physiologisch-chemisches Institut der Universitaet, Hoppe-Seyler-Strasse 4, D-72076, Tuebingen**Germany
JOURNAL: European Journal of Biochemistry 267 (16):p4912-4916 August, **2000**

MEDIUM: print
ISSN: 0014-2956
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The cells of the adult human brain consume apprxeq20% of the oxygen utilized by the body although the brain comprises only 2% of the body weight. Reactive oxygen species, which are produced continuously during oxidative metabolism, are generated at high rates within the brain. Therefore, the defense against the toxic effects of reactive oxygen species is an essential task within the brain. An important component of the cellular detoxification of reactive oxygen species is the antioxidant glutathione. The main focus of this short **review** is recent results on glutathione metabolism of brain astrocytes and neurons in **culture**. These two types of **cell** prefer different extracellular precursors for glutathione. Glutathione is involved in the disposal of exogenous peroxides by astrocytes and neurons. In coculture astrocytes protect neurons against the toxicity of reactive oxygen species. One mechanism of this interaction is the supply by astrocytes of glutathione precursors to neurons.

2000

11/3,AB/32 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12565916 BIOSIS NO.: 200000319418
Dorsal unpaired median neurones in the insect central nervous system: Towards a better understanding of the ionic mechanisms underlying spontaneous electrical activity.
AUTHOR: Grolleau Francoise; Lapied Bruno
AUTHOR ADDRESS: (a)Laboratoire de Neurophysiologie, UPRES EA 2647 (RCIM), Universite d'Angers, Rue Haute de Reculee, F-49045, Angers Cedex**France
JOURNAL: Journal of Experimental Biology 203 (11):p1633-1648 June, **2000**
MEDIUM: print
ISSN: 0022-0949
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The efferent dorsal unpaired median (DUM) neurones, which include octopaminergic neurones, are among the most intensively studied neurones in the insect central nervous system. They differ from other insect neurones in generating endogenous spontaneous overshooting action potentials. The second half of the 1980s is certain to be considered a turning point in the study of the ion channels underlying the electrical activity of DUM neurones. Recent advances made using the patch-clamp technique have stimulated an increasing interest in the understanding of the biophysical properties of both voltage-dependent and voltage-independent ion channels. Patch-clamp studies of DUM neurones in **cell culture** demonstrate that these neurones express a wide variety of ion channels. At least five different types of K+ channel have been identified: inward rectifier, delayed rectifier and A-like channels as well as Ca2+- and Na+-activated K+ channels. Moreover, besides voltage-dependent Na+ and Ca2+-sensitive Cl- channels, DUM neurones also express four types of Ca2+ channel distinguished on the basis of their kinetics, voltage range of activation and pharmacological profile. Finally, two distinct resting Ca2+ and Na+ channels have been shown to be

involved in maintaining the membrane potential and in regulating the firing pattern. In this **review**, we have also attempted critically to evaluate these existing ion channels with regard to their specific functions in the generation of the different phases of the spontaneous electrical activity of the DUM neurone.

2000

11/3,AB/33 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12565847 BIOSIS NO.: 200000319349
Ras-related and MAPK signalling in neuronal plasticity and memory formation.
AUTHOR: Mazzucchelli C; Brambilla R
AUTHOR ADDRESS: (a)San Raffaele Scientific Institute, via Olgettina 58, I-20132, Milano**Italy
JOURNAL: CMLS Cellular and Molecular Life Sciences 57 (4):p604-611 April, **2000**
MEDIUM: print
ISSN: 1420-682X
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Ras-related guanosine triphosphatases (GTPases) couple receptor activity to a number of intra-cellular signalling events culminating in the control of **cell** morphology and gene transcription. In **culture** cells, the best-understood Ras-dependent signalling pathway involves the mitogen-activated protein kinase/extracellular-regulated kinase (MAPK/ERK) cascade. A growing body of evidence has recently been accumulating to suggest a crucial role of Ras and MAPK signalling in neuronal functions connected to synaptic plasticity. In the present **review** article we discuss the experimental basis supporting the notion that the Ras/MAPK pathway interacts with other synaptic mechanisms to regulate invertebrate and vertebrate behavioural responses such as those implicated in learning and memory processes.

2000

11/3,AB/34 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12518429 BIOSIS NO.: 200000271931
Mechanisms for neuronal degeneration in amyotrophic lateral sclerosis and in models of motor neuron death (**Review**).
AUTHOR: Martin Lee J(a); Price Ann C; Kaiser Adeel; Shaikh Arif Y; Liu Zhiping
AUTHOR ADDRESS: (a)Department of Pathology, Johns Hopkins University School of Medicine, 720 Rutland Avenue, 558 Ross Building, Baltimore, MD, 21205-2196**USA
JOURNAL: International Journal of Molecular Medicine 5 (1):p3-13 Jan., **2000**
MEDIUM: print.
ISSN: 1107-3756
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Amyotrophic lateral sclerosis (ALS), also referred to as motor neurone disease, is a fatal neurological disease that is characterized clinically by progressive muscle weakness, muscle atrophy, and eventual paralysis. The neuropathology of ALS is primary degeneration of upper (motor cortical) and lower (brainstem and spinal) motor neurons. The amyotrophy refers to the neurogenic atrophy of affected muscle groups, and the lateral sclerosis refers to the hardening of the lateral white matter funiculus in spinal cord (corresponding to degeneration of the corticospinal tract) found at autopsy. Because the mechanisms for the motor neuron degeneration in ALS are not understood, this disease has no precisely known causes and no effective treatments. Very recent studies have identified that the degeneration of motor neurons in ALS is a form of apoptotic **cell** death that may occur by an abnormal programmed **cell** death (PCD) mechanism. In order to treat ALS effectively, we need to understand the mechanisms for motor neuron apoptosis more completely. Future studies need to further identify the signals for PCD activation in neurons as they relate to the pathogenesis of ALS and to clarify the molecular pathways leading to motor neuron apoptosis in animal and **cell culture** model systems. These studies should lead to a better understanding of motor neuron death and to the design of new therapeutic experiments critical for the future treatment of ALS.

2000

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4/3,AB/1 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09989945 98420327 PMID: 9749879
Pathophysiology of the kallikrein-kinin system in mammalian nervous tissue.
Raidoo D M; Bhoola K D
Department of Physiology, Faculty of Medicine, University of Natal, Durban, South Africa.
Pharmacology & therapeutics (ENGLAND) Aug **1998**, 79 (2) p105-27
, ISSN 0163-7258 Journal Code: 7905840
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The nervous system and peripheral tissues in mammals contain a large number of biologically active peptides and proteases that function as neurotransmitters or neuromodulators in the nervous system, as hormones or cellular mediators in peripheral tissue, and play a role in human neurological diseases. The existence and possible functional relevance of bradykinin and kallidin (the peptides), kallikreins (the proteolytic enzymes), and kininases (the peptidases) in neurophysiology and neuropathological states are discussed in this **review** . Tissue kallikrein, the major cellular kinin-generating enzyme, has been localised in various areas of the mammalian brain. Functionally, it may assist also in the normal turnover of brain proteins and the processing of peptide-hormones, neurotransmitters, and some of the nerve growth factors that are essential for normal neuronal function and synaptic transmission. A specific class of kininases, peptidases responsible for the rapid degradation of kinins, is considered to be identical to enkephalinase A. Additionally, kinins are known to mediate inflammation, a cardinal feature of which is pain, and the clearest evidence for a primary neuronal role exists so far in the activation by kinins of peripherally located nociceptive receptors on C-fibre terminals that transmit and modulate pain perception. Kinins are also important in vascular homeostasis, the release of excitatory amino acid neurotransmitters, and the modulation of cerebral cellular immunity. The two kinin receptors, B2 and B1, that modulate the cellular actions of kinins have been demonstrated in animal neural tissue, neural cells in **culture**, and various areas of the human brain. Their localisation in **glial** tissue and neural centres, important in the regulation of cardiovascular homeostasis and nociception, suggests that the kinin system may play a functional role in the nervous system.

4/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09806066 98239202 PMID: 9579599
Ependymal and choroidal cells in **culture**: characterization and functional differentiation.
Gabrion J B; Herbute S; Bouille C; Maurel D; Kuchler-Bopp S; Laabich A; Delaunoy J P
UMR CNRS 5539, Universite Montpellier 2, France. Jacqueline.Gabrion@snv.jussieu.fr
Microscopy research and technique (UNITED STATES) Apr 15 **1998**, 41 (2) p124-57, ISSN 1059-910X Journal Code: 9203012
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
During the past 10 years, our teams developed long-term primary cultures of ependymal cells derived from ventricular walls of telencephalon and hypothalamus or choroidal cells (modified ependymal cells) derived from plexuses dissected out of fetal or newborn mouse or rat brains. Cultures were established in serum-supplemented or chemically defined media after seeding on serum-, fibronectin-, or collagen-laminin-coated plastic dishes or semipermeable inserts. To identify and characterize cell types growing in our cultures, we used morphological features provided by phase contrast, scanning, and transmission electron microscopy. We used antibodies against intermediate filament proteins (vimentin, **glial** fibrillary acidic protein, cytokeratin, desmin, neurofilament proteins), actin, myosin, ciliary rootlets, laminin, and fibronectin in single or double immunostaining, and monoclonal antibodies against epitopes of ependymal or endothelial cells, to recognize ventricular wall cell types with immunological criteria. Ciliated or nonciliated ependymal cells in telencephalic cultures, tanycytes and ciliated and nonciliated ependymal cells in hypothalamic cultures always exceeded 75% of the cultured cells under the conditions used. These cells were characterized by their cell shape and epithelial organization, by their apical differentiations observed by scanning and transmission electron microscopy, and by specific markers (e.g., **glial** fibrillary acidic protein, ciliary rootlet proteins, DARPP 32) detected by immunofluorescence. All these cultured ependymal cell types remarkably resembled in vivo ependymocytes in terms of molecular markers and ultrastructural features. Choroidal cells were also maintained for several weeks in **culture**, and abundantly expressed markers were detected in both choroidal tissue and **culture** (Na+-K+-dependent ATPase, DARPP 32, G proteins, ANP receptors). In this **review**, the **culture** models we developed (defined in terms of biological material, media, substrates, duration, and subculturing) are also compared with those developed by other investigators during the last 10 years. Focusing on morphological and functional approaches, we have shown that these **culture** models were suitable to investigate and provide new insights on (1) the gap junctional communication of ependymal, choroidal, and astroglial cells in long-term primary cultures by freeze-fracture or dye transfer of Lucifer Yellow CH after intracellular microinjection; (2) some ionic channels; (3) the hormone receptors to tri-iodothyronine or atrial natriuretic peptides; (4) the regulatory effect of tri-iodothyronine on glutamine synthetase expression; (5) the endocytosis and transcytosis of proteins; and (6) the morphogenetic effects of galactosyl-ceramide. We also discuss new insights provided by recent results reported on in vitro ependymal and choroidal expressions of neuropeptide-processing enzymes and neurosecretory proteins or choroidal expression of transferrin regulated through serotoninergic activation.

4/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09788286 98204643 PMID: 9545082
Cell **culture** models for reactive gliosis: new perspectives.
Wu V W; Schwartz J P
Molecular Genetics Section, Clinical Neuroscience Branch, National Institute of Neurological Disorders and Stroke, Bethesda, Maryland 20892-1279, USA.
Journal of neuroscience research (UNITED STATES) Mar 15 **1998**, 51 (6) p675-81, ISSN 0360-4012 Journal Code: 7600111
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Reactive gliosis, which occurs in response to any damage or disturbance to the central nervous system, has been recognized for many years, but is still not completely understood. The hallmark is the increased expression of **glial** fibrillary acidic protein (GFAP), yet studies in GFAP knockout mice suggest that GFAP may not be required for an astrocyte to become hypertrophic. In this **review**, we describe a series of tissue **culture** models that have been established in order to address: 1) the biochemical phenotype of reactive astrocytes; 2) the factor and/or cell responsible for induction of gliosis; 3) the mechanisms by which one might block the induction. These models range from cultures of astrocytes, both neonatal and adult, to co-cultures of astrocytes with either neurons or microglia, to organ cultures. None is ideal: each addresses a different set of questions, but taken together, they are beginning to provide useful information which should allow a better understanding of the plasticity response of astrocytes to brain injury.

4/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09717910 98141348 PMID: 9482244
Brain injury and growth inhibitory factor (GIF)--a minireview.
Hozumi I; Inuzuka T; Tsuji S
Department of Neurology, Brain Research Institute, Niigata University, Niigata City, Japan.
Neurochemical research (UNITED STATES) Mar **1998**, 23 (3) p319-28, ISSN 0364-3190 Journal Code: 7613461
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Growth inhibitory factor (GIF) is a small (7 kDa), heat-stable, acidic, hydrophilic metallothionein (MT)-like protein. GIF inhibits the neurotrophic activity in Alzheimer's disease (AD) brain extracts on neonatal rat cortical neurons in **culture**. GIF has been shown to be drastically reduced and down-regulated in AD brains. In neurodegenerative diseases in humans, GIF expression levels are reduced whereas GFAP expression levels are markedly induced in reactive astrocytes. Both GIF and GIF mRNA are present at high levels in reactive astrocytes following acute experimental brain injury. In chronological observations the level of GIF was found to increase more slowly and remain elevated for longer periods than that of **glial** fibrillary acidic protein (GFAP). These differential patterns and distribution of GIF and GFAP seem to be important in understanding the mechanism of brain tissue repair. The most important point concerning GIF in AD is not simply the decrease in the level of expression throughout the brain, but the drastic decrease in the level of expression in reactive astrocytes around senile plaques in AD. Although what makes the level of GIF decrease drastically in reactive astrocytes in AD is still unknown, supplements of GIF may be effective for AD, based on a **review** of current evidence. The processes of tissue repair following acute brain injury are considered to be different from those in AD from the viewpoint of reactive astrocytes.

4/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08861151 96226648 PMID: 8679514
Neurons and **glial** cells of the enteric nervous system: studies in tissue **culture**.
Hanani M
Laboratory of Experimental Surgery, Hadassah University Hospital, Mount Scopus, Jerusalem, Israel.
Journal of basic and clinical physiology and pharmacology (ENGLAND) Jul-Sep **1993**, 4 (3) p157-79, ISSN 0792-6855 Journal Code: 9101750
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The enteric nervous system (ENS) has been recognized as the main component in regulating the function of the digestive tract and as a model for studying neuronal physiology and pharmacology. Most of the present knowledge on the ENS was derived from in vitro studies on freshly isolated plexuses. In 1978 the first study on cultured myenteric neurons was published and since then there has been a growing interest in this method. Several different **culture** preparations have been introduced, including the recent development of cultures from adult guinea-pigs and humans. This **review** summarizes the findings which have been made using cultured enteric neurons and glia. The main topics that are described are the role of the extracellular matrix and of hormones on neuronal growth, neuron-glia interactions, release of neuropeptides and their actions on neurons and co-transmission between neurons.

4/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08707190 96058750 PMID: 8531218
Excitatory amino acid receptors in glia: different subtypes for distinct functions?
Gallo V; Russell J T
Laboratory of Cellular and Molecular Neurophysiology, National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, Maryland 20892, USA.
Journal of neuroscience research (UNITED STATES) Sep 1 **1995**, 42 (1) p1-8, ISSN 0360-4012 Journal Code: 7600111
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
It is now well established that expression of voltage- and ligand-gated ionic channels, as well as G protein-coupled receptors, is not a property unique to neurons, but is also shared by macroglial cells (astrocytes and oligodendrocytes). These **glial** cells can receive a variety of signals from neurons at different stages of their development. Activation of membrane receptors may affect **glial** cell activity, proliferation, maturation, and survival through a complex cascade of intracellular events leading to long-term changes in **glial** cell phenotype and functional organization. Here we **review** the experimental evidence for glutamate receptor expression in **glial** cells in **culture** and in situ, and the molecular and functional properties of these receptors. We also describe some experimental models that identify possible functions of glutamate receptors in glia. Now that the existence of glutamate receptors in glia has been unambiguously demonstrated, future research will have to 1) determine which receptor subtypes are expressed in macroglial cells in

vivo; 2) analyze, in adequate experimental models, the short- and long-term changes produced by glutamate receptor activation in glia; and 3) establish whether these receptors play a role in neuron-glia communication in the brain.

4/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08471314 95223412 PMID: 7708144
Glial differentiation: a **review** with implications for new directions in neuro-oncology.
Linskey M E; Gilbert M R
Department of Neurological Surgery, University of Pittsburgh School of Medicine, Pennsylvania.
Neurosurgery (UNITED STATES) Jan **1995**, 36 (1) p1-21; discussion 21-2, ISSN 0148-396X Journal Code: 7802914
Contract/Grant No.: 5-T32 DK-07458; DK; NIDDK; 7 K08NS-01339-03; NS; NINDS
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Major advances in cell **culture** techniques, immunology, and molecular biology during the last 10 years have led to significant progress in understanding the process of normal **glial** differentiation. This article summarizes our current understanding of the cellular and molecular basis of **glial** differentiation based on data obtained in cell **culture** and reviews current hypotheses regarding the transcriptional control of the gene switching that controls differentiation. Understanding normal **glial** differentiation has potentially far-reaching implications for developing new forms of treatment for patients with **glial** neoplasms. If oncogenesis truly involves a blockage or a short circuiting of the differentiation process in adult **glial** progenitor cells, or if it results from dedifferentiation of previously mature cells, then a clear understanding of differentiation may provide a key to understanding and potentially curtailing malignancy. Differentiation agents represent a relatively new class of drugs that effect cellular gene transcription at the nuclear level, probably through alterations in chromatin configuration and/or differential gene induction. These exciting new agents may provide a means of preventing the dedifferentiation of low-grade gliomas or inducing malignant glioma cells to differentiate with minimal toxicity. In the future, genetic therapy has the potential of more specifically rectifying the defect in genetic control that led to oncogenesis in any given tumor.

4/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07930876 94065904 PMID: 8246054
Central nervous system gangliogliomas. Part 1: Pathology.
Miller D C; Lang F F; Epstein F J
Department of Pathology (Division of Neuropathology), New York University Medical Center, New York.
Journal of neurosurgery (UNITED STATES) Dec **1993**, 79 (6) p859-66, ISSN 0022-3085 Journal Code: 0253357
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Histopathological features that suggest the diagnosis of ganglioglioma require, in most cases, confirmation by special stains to distinguish these tumors from other gliomas. For this purpose, immunostaining for

synaptophysin, which has previously been shown to selectively label the cell surface of neoplastic ganglion cells, was used to retrospectively examine glioma tumor specimens. Sixty-three cases of ganglioglioma were identified. The files of the Division of Neuropathology of New York University Medical Center contained 45 tumors that had been diagnosed as ganglioglioma, of which 42 were verified by synaptophysin; three cases were reclassified, two as astrocytomas and one as a gangliocytic paraganglioma. Thus, a tumor identified as ganglioglioma based on other criteria was likely to be a ganglioglioma. The other 21 cases of gangliogliomas were originally diagnosed as astrocytoma or mixed glioma, but were shown by synaptophysin staining to be gangliogliomas. In some cases the ultimate diagnosis was obtained after radical surgery provided relatively abundant amounts of tissue, thereby limiting sampling errors, in contrast to the biopsies from which the original diagnoses were made. Histopathological **review** of these cases demonstrated that four features represent important clues to the correct diagnosis: 1) clusters of large cells potentially representing neurons (without such cells the tumor cannot be classified as a ganglioglioma); 2) no perineuronal clustering of the **glial** cells around the alleged neoplastic neurons; 3) fibrosis (desmoplasia); and 4) calcification. Binucleate neurons, previously suggested to be common in gangliogliomas, were not frequently found in this series, and lymphocytic infiltrates, while common, are so often found in other tumors that they gave no specific hint that any single neoplasm was a ganglioglioma. The **glial** elements were astrocytic in all cases, except that one tumor also had oligodendroglial and ependymal patterns. Four tumors also had small mature neurons, as seen in neurocytomas. Cells from one tumor were successfully grown in short-term tissue **culture**; the **culture** contained large dividing neurons with synaptophysin immunoreactivity as well as smaller dividing cells, demonstrating that the neuronal cells are a proliferating element in gangliogliomas.

4/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07767651 93295526 PMID: 8515840
Molecular profile of reactive astrocytes--implications for their role in neurologic disease.
Eddleston M; Mucke L
Department of Neuropharmacology, Scripps Research Institute.
Neuroscience (ENGLAND) May **1993**, 54 (1) p15-36, ISSN 0306-4522 Journal Code: 7605074
Contract/Grant No.: MHA47680; MH; NIMH
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The central nervous system responds to diverse neurologic injuries with a vigorous activation of astrocytes. While this phenomenon is found in many different species, its function is obscure. Understanding the molecular profile characteristic of reactive astrocytes should help define their function. The purpose of this **review** is to provide a summary of molecules whose levels of expression differentiate activated from resting astrocytes and to use the molecular profile of reactive astrocytes as the basis for speculations on the functions of these cells. At present, reactive astrocytosis is defined primarily as an increase in the number and size of cells expressing **glial** fibrillary acidic protein. In vivo, this increase in **glial** fibrillary acidic protein-positive cells reflects predominantly phenotypic changes of resident astroglia rather than migration or proliferation of such cells. Upon activation, astrocytes upmodulate the expression of a large number of molecules. From this molecular profile it becomes apparent that reactive astrocytes may benefit the injured nervous system by participating in diverse biological processes. For example, upregulation of proteases and protease inhibitors

could help remodel the extracellular matrix, regulate the concentration of different proteins in the neuropil and clear up debris from degenerating cells. Cytokines are key mediators of immunity and inflammation and could play a critical role in the regulation of the blood-central nervous system interface. Neurotrophic factors, transporter molecules and enzymes involved in the metabolism of excitotoxic amino acids or in the antioxidant pathway may help protect neurons and other brain cells by controlling neurotoxin levels and contributing to homeostasis within the central nervous system. Therefore, an impairment of astroglial performance has the potential to exacerbate neuronal dysfunction. Based on the synopsis of studies presented, a number of issues become apparent that deserve a more extensive analysis. Among them are the relative contribution of microglia and astrocytes to early wound repair, the characterization of astroglial subpopulations, the specificity of the astroglial response in different diseases as well as the analysis of reactive astrocytes with techniques that can resolve fast physiologic processes. Differences between reactive astrocytes in vivo and primary astrocytes in **culture** are discussed and underline the need for the development and exploitation of models that will allow the analysis of reactive astrocytes in the intact organism.

4/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07579015 93106299 PMID: 1468601
The 5 alpha-reductase in the brain: molecular aspects and relation to brain function.
Celotti F; Melcangi R C; Martini L
Department of Endocrinology, University of Milan, Italy.
Frontiers in neuroendocrinology (UNITED STATES) Apr **1992**, 13 (2) p163-215, ISSN 0091-3022 Journal Code: 7513292
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
All the classes of hormonal steroids physiologically produced in the body (androgens, estrogens, progestagens, and corticosteroids) are able to exert important effects on the brain, but the mechanisms of their actions are not always well understood. Steroids may interact with intracellular receptors to activate the genome, but some of their effects are probably extragenomic and involve interactions with cellular membranes. Moreover, not all the steroids act always in their native molecular form; a large group of them must actually be transformed into "active" metabolites. This may occur at the level of their respective target structures. For example, androgens are metabolized in the brain into estrogens and into 5 alpha-reduced androgens, like 5 alpha-androstan-17 beta-ol-3-one (dihydrotestosterone; DHT) and 5 alpha-androstan-3 alpha, 17 beta-diol (3 alpha-diol). Progesterone, and possibly corticosteroids, may also be transformed into their corresponding 5 alpha-reduced metabolites. Also the cellular target (neurons and/or **glial** cells) of the hormonal steroids in the brain is not always clear. This **review** analyzes in detail one of the two major enzymatic systems that transform steroids in the brain, namely the 5 alpha-reductase-3 alpha-(3 beta)-hydroxysteroid dehydrogenase pathway. An active 5 alpha-reductase-3 alpha-hydroxysteroid dehydrogenase system is widely distributed in practically all CNS structures in all phases of development. In the brain, this enzymatic system is not regulated by castration or sex steroid administration; furthermore, neural inputs seem to be ineffective at the hypothalamic level. A recent interesting finding is the presence of high concentrations of the 5 alpha-reductase in the white matter. This probably is due to the fact that the white matter is particularly rich in myelin membranes, with which the enzymatic activity appears to be associated. An active 5 alpha-reductase activity has also been shown to be present in peripheral myelinated nerves. The localization in myelin membranes may suggest a possible involvement of 5 alpha-reduced

metabolites of the different steroids in the process of myelination. The presence of the 5 alpha-reductase was analyzed in neurons, astrocytes, and oligodendrocytes isolated from the brains of male rats, as well as in neurons and **glial** cells grown in **culture**. Neurons appear to be more active than **glial** cells in converting testosterone into DHT. Only neurons possess aromatase activity.(ABSTRACT TRUNCATED AT 400 WORDS)

4/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

07378902 92293430 PMID: 1351254
New trend in neuroscience: low-power laser effect on peripheral and central nervous system (basic science, preclinical and clinical studies).
Rochkind S; Ouaknine G E
Department of Neurosurgery, Tel-Aviv Sourasky Medical Center, Tel-Aviv University, Israel.
Neurological research (ENGLAND) Mar **1992**, 14 (1) p2-11, ISSN 0161-6412 Journal Code: 7905298
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The present **review** summarizes findings in our continuing study of the use of low-power laser irradiation (LPLI) in the treatment of severely injured peripheral (PNS) and central nervous systems (CNS). The radiation method was proposed by Rochkind and has been modified over the last 13 years. LPLI in specific wavelengths and energy density maintains the electrophysiological activity of severely injured peripheral nerve in rats, preventing scar formation (at injury site) as well as degenerative changes in the corresponding motor neurons of the spinal cord, thus accelerating regeneration of the injured nerve. Laser irradiation applied to the spinal cord of dogs following severe spinal cord injury and implantation of a segment of the peripheral nerve into the injured area diminished **glial** scar formation, induced axonal sprouting in the injured area and restoration of locomotor function. The use of laser irradiation in mammalian CNS transplantation shows that laser therapy prevents extensive **glial** scar formation (a limiting factor in CNS regeneration) between a neural transplant and the host brain or spinal cord. Abundant capillaries developed in the laser-irradiated transplants, and was of crucial importance in their survival. Intraoperative clinical use of laser therapy following surgical treatment of the tethered spinal cord (resulting from myelomeningocele, lipomyelomeningocele, thickened filum terminale or fibrous scar) increases functional activity of the irradiated spinal cord. In a previous experimental work, we showed that direct laser treatment on nerve tissue promotes restoration of the electrophysiological activity of the severely injured peripheral nerve, prevents degenerative changes in neurons of the spinal cord and induces proliferation of astrocytes and oligodendrocytes. This suggested a higher metabolism in neurons and improved ability for myelin production under the influence of laser treatment. The tethering of the spinal cord causes mechanical damage to neuronal cell membranes leading to metabolic disturbances in the neurons. For this reason, we believe that using LPLI may improve neuronal metabolism, prevent neuronal degeneration and promote improved spinal cord function and repair. The possible mechanism of LPLI is investigated. Using electron paramagnetic resonance in cell **culture** models, we found that at low radiation doses, singlet oxygen is produced by energy transfer from porphyrin (not cytochrome as commonly assumed) which is known to be present in the cell. At low concentration, singlet oxygen can modulate biochemical processes taking place in the cell and trigger accelerated cell division. On the other hand, at high concentration, singlet oxygen damages the cell.(ABSTRACT TRUNCATED AT 400 WORDS)

4/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06927747 91236229 PMID: 1827776
Division of astroblasts and oligodendroblasts in postnatal rodent brain: evidence for separate astrocyte and oligodendrocyte lineages.
Skoff R P; Knapp P E
Department of Anatomy and Cell Biology, Wayne State University School of Medicine, Detroit, Michigan 48201.
Glia (UNITED STATES) **1991**, 4 (2) p165-74, ISSN 0894-1491
Journal Code: 8806785
Contract/Grant No.: NS 15338; NS; NINDS
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
What precursor cells are the source of the macroglia generated during postnatal development? In order to answer this question, we studied the expression of **glial** specific antigens in proliferating neuroglia in postnatal rodent brain and optic nerve. Immunocytochemistry using antibodies to oligodendrocyte (OL) specific markers (sulfatide and galactocerebroside) and an astrocyte (AS) specific marker (**glial** fibrillary acidic protein) was combined with thymidine autoradiography. During the first week of postnatal development when most ASs are being generated, one third to one half of the proliferating cells in the optic system are positive for **glial** fibrillary acidic protein after a 1 h injection of thymidine (Skoff, Dev. Biol., 139:149-168, 1990). During the second postnatal week when OLs are being generated, 30 to 100% of the proliferating cells in presumptive white matter tracts are sulfatide positive and at least 10% are galactocerebroside positive. This finding demonstrates that ASs and OLs divide during postnatal development. These results confirm previous electron microscopic autoradiographic studies showing that the vast majority of proliferating cells in postnatal rat optic nerve have the morphologic characteristics of differentiating ASs or OLs (Skoff, J. Comp. Neurol., 169:291-312, 1976). Since proliferating ASs (astroblasts) and OLs (oligodendroblasts) constitute the majority of the dividing cells at the time that ASs and OLs are being generated, these glioblasts must be the major source for the macroglia generated postnatally. The findings strongly suggest that separate lineages exist for ASs and OLs during postnatal development. There is no compelling in vivo evidence for a bipotential progenitor cell that generates the majority of OLs and certain ASs in postnatal rodent brain. There may, of course, be distinct lineages for the subtypes of ASs and possibly even for subtypes of OLs. We **review** the concepts of commitment and plasticity and apply these terms to **glial** differentiation. In situ, the presence of oligodendroblasts and astroblasts demonstrates the COMMITMENT of proliferating cells to a specific **glial** lineage during normal development. **Culture** conditions may provide an environment that permits proliferating **glial** cells to vacillate in their selection of a specific lineage. This situation demonstrates developmental PLASTICITY and the ability of glia to adapt to an altered environment. Whether committed **glial** cells in situ can be induced to switch their lineage when normal CNS conditions are altered is an intriguing question that remains to be answered.

4/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06927745 91236227 PMID: 1709616
Tracing **glial** cell lineages in the mammalian forebrain.
Goldman J E; Vaysse P J
Department of Pathology, Columbia University College of Physicians and Surgeons, New York, New York 10032.

Glia (UNITED STATES) **1991**, 4 (2) p149-56, ISSN 0894-1491
Journal Code: 8806785
Contract/Grant No.: NS 17125; NS; NINDS
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Astrocytes and oligodendrocytes emerge in late gestational and early post-natal development in the mammalian CNS. The nature, and number, of progenitors for each **glial** type is a central question. This **review** will focus upon several unresolved issues relating to **glial** cell lineages and describe new methods to try to illuminate these issues further: 1) How can developmental patterns by which immature neuroectodermal cells give rise to classes of neurons and glia be understood in the context of lineage? 2) What are the lineage relationships among the various cell classes, how many **glial** lineages are there in the developing CNS, and how can recent methods of clonal analysis using stable markers be used to clarify lineage patterns? 3) Do patterns of gliogenesis vary in different regions of the CNS? 4) How do patterns of gliogenesis observed in vitro relate to those in vivo?

4/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06809033 91091318 PMID: 2486601
Recent advances in neural cell **culture**]
Kim S U
Department of Medicine, University of British Columbia, Vancouver, Canada.
Human cell : official journal of Human Cell Research Society (JAPAN) Jun **1989**, 2 (2) p122-31, ISSN 0914-7470 Journal Code: 8912329
Document type: Journal Article ; English Abstract
Languages: JAPANESE
Main Citation Owner: NLM
Record type: Completed

Cells isolated from the avian and mammalian central and peripheral nervous system and cultured in vitro provide an opportunity to study in situ properties of neurons and **glial** cells under relatively simple and carefully controlled conditions. Since Harrison's success in maintaining in vitro embryonic frog spinal cord 80 years ago, neural tissue **culture** has developed into an important and versatile discipline of neuroscience. The techniques developed in the past fall into four broad classes: Explant cultures, which are explanted from specific neuroanatomic loci to substrates as small tissue fragments. Dissociated cell cultures, which involve the seeding of enzymatically or mechanically dispersed cells on various attachment substrates. Reaggregate cultures, which require re-association of dissociated cells into small aggregates. Purified cell populations, which are prepared by the isolation of different cell types by gradient centrifugation or other separation techniques. These cultures have been utilized in studying various aspects of brain development and function. In this **review** several areas of significant and stimulating development in neural cell **culture** have been documented. They include formulation of serum-free medium, effects of growth factors, utilization of cell type-specific markers, and isolation and **culture** of purified neuronal/**glial** cells.

4/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06569570 90239845 PMID: 1692169
The use of cell lines in neurobiology.
Lendahl U; McKay R D

Department of Brain and Cognitive Sciences, Massachusetts Institute of Technology, Cambridge 02142.
Trends in neurosciences (ENGLAND) Apr **1990**, 13 (4) p132-7, ISSN 0166-2236 Journal Code: 7808616
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The mature nervous system is made up of a large number of terminally differentiated neuronal and **glial** cell types which develop from precursor cells in the embryonic nervous system. Many aspects of the differentiation pathways leading to the formation of neurons and glia remain elusive because of the cellular and molecular complexity of the brain, with cells of different types intermingled and differentiating at different times. One way to reduce the complexity is to study particular developmental stages and steps in neuronal differentiation in cell lines, i.e. clonal, homogeneous populations of cells that can be grown indefinitely in vitro. Urban Lendahl and Ronald McKay discuss how cell lines are used to dissect the cellular differentiation of the nervous system. Recent technical progress may allow the construction of 'custom-made' cell lines from different regions and developmental stages in the nervous system. Such cell lines retain features of the cells from which they originated and make possible detailed molecular studies of features only transiently present in the developing brain. New strategies are being developed which can be used to assess the effect of genetic changes in cell lines both in tissue **culture** and in the whole animal. This **review** attempts to show that cell lines are not a 'reductio ad absurdum' but an additional and critical tool in understanding the genetic contribution to the organization and function of the brain.

4/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06147211 89234233 PMID: 2654147
Proteolytic regulation of neurite outgrowth from neuroblastoma cells by thrombin and protease nexin-1.
Cunningham D D; Gurwitz D
Department of Microbiology and Molecular Genetics, College of Medicine, University of California, Irvine 92717.
Journal of cellular biochemistry (UNITED STATES) Jan **1989**, 39 (1) p55-64, ISSN 0730-2312 Journal Code: 8205768
Contract/Grant No.: CA 12306; CA; NCI
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

This **review** summarizes studies on the reciprocal regulation of neuroblastoma neurite outgrowth by thrombin and protease nexin-1 (PN-1). PN-1 recently was shown to possess the same deduced amino acid sequence as the **glial** -derived neurite-promoting factor. The neurite outgrowth activity of PN-1 depends on its ability to inhibit thrombin. Thrombin not only blocks the neurite outgrowth activity of PN-1, but it also brings about neurite retraction in the presence of PN-1. Thrombin also produces neurite retraction in the absence of PN-1 and other regulatory factors. This suggests that its activity is due to a direct action on cells. The neurite retraction by thrombin depends on its proteolytic activity. It does not occur with the other serine proteases that have been tested, indicating that it is a specific effect and is not due to a general proteolytic effect that could detach neurites from the **culture** dish. Serum brings about neurite retraction in certain neuroblastoma cells and primary neuronal cultures; most of this activity is due to residual thrombin in the serum. Together, these results suggest that PN-1 and thrombin (or a thrombin-like protease) play a role in regulation of neurite outgrowth.

4/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06070295 89159920 PMID: 3068600
Retinoblastoma cells in tissue **culture**.
Campbell M; Chader G J
Laboratory of Retinal Cell and Molecular Biology, National Eye Institute, Bethesda, MD.
Ophthalmic paediatrics and genetics (NETHERLANDS) Nov **1988**, 9 (3) p171-99, ISSN 0167-6784 Journal Code: 8206832
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
This **review** summarizes and discusses research on retinoblastoma (Rb) cells in tissue **culture**. Retinoblastoma is an intraocular tumor of early childhood which is believed to originate from the primitive multipotential neuroectoderm of the optic cup region. The application of tissue **culture** techniques to the study of Rb cells permits detailed studies of the biology of this tumor. Classic studies have primarily focussed on growth and metastatic potential of Rb cells. Y-79 Rb cells, for example, have a short doubling time in vitro as well as aggressively growing in the anterior chambers of athymic 'nude' mice. Such active growth may result from secretion of a Retinoblastoma Derived Growth Factor (RDGF) by the cells. Several natural agents have now been shown to halt Rb cell growth in vitro. Among these are the fatty acid, butyrate, and two retinoids: retinol and retinoic acid. Interestingly, the retinoids have different mechanisms of action. Cultured Y-79 and WERI cells appear to be multipotential in that they exhibit both neuronal- and **glial**-like characteristics. Natural agents such as cyclic AMP and butyrate can induce the cells to differentiate along either neuronal or **glial** cell lines as assessed morphologically and immunocytochemically. Of interest is that combination of agents such as butyrate and laminin, an extracellular attachment protein, yield totally different morphologies, in this case, pigment epithelial in nature. Tissue **culture** studies thus not only show the primitive, multipotential nature of the Rb cells but their great plasticity as well. Such studies are also useful in elucidating the multiple factors (e.g., substrata and soluble agents) which code for normal retinal development from embryo to adult.

4/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05998342 89068036 PMID: 2535715
Phenotypic analysis of four human medulloblastoma cell lines and transplantable xenografts.
He X M; Skapek S X; Wikstrand C J; Friedman H S; Trojanowski J Q; Kemshead J T; Coakham H B; Bigner S H; Bigner D D
Department of Pathology, Duke University Medical Center, Durham, NC 27710.
Journal of neuropathology and experimental neurology (UNITED STATES) Jan **1989**, 48 (1) p48-68, ISSN 0022-3069 Journal Code: 2985192R
Contract/Grant No.: 1 K07NS00958; NS; NINDS; 1 NINCDS NS20023-03; NS; NINDS; CA11898; CA; NCI; +
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
An extensive panel of monoclonal antibodies (MAb) and monospecific antisera reactive against neuroectodermal-, neuronal-, **glial**-, and lymphoid-associated antigens, extracellular matrix, HLA, and cell-surface

receptors was used to characterize the phenotype of four continuous, karyotypically distinct medulloblastoma cell lines and transplantable xenografts. All four cell lines demonstrated significant reactivity with anti-neuroectodermal-associated MAb. No apparent pattern of reactivity with anti-lymphoid MAb was seen; notably, there was a uniform absence of detectable Thy-1. **Review** of the complete antibody reactivity profile revealed a dichotomy between lines TE-671 and Daoy and lines D283 Med and D341 Med, which have been previously shown to express neurofilament protein in **culture** and xenografts, and to exhibit neuroblastic morphological features in biopsy and xenograft tissue sections. TE-671 and Daoy reacted with the MAb directed against tenascin, epidermal growth factor (EGF) receptor, HLA-A,B epitopes, beta 2-microglobulin and 5/8 of the glioma-associated antigens, but did not react with the anti-neurofilament protein (NFP) MAb. D283 Med and D341 Med expressed NFP but did not react with MAb against tenascin, EGF receptor, HLA-A,B epitopes, beta 2-microglobulin or 6/8 and 7/8 (respectively) of the glioma-associated antigens. The observed phenotypic differences provide a conceptual framework for investigating basic differences in the biological behavior of medulloblastoma. Moreover, the subdivisions can be evaluated for prospective value in tissue diagnosis, cerebrospinal fluid cytology and antibody-mediated imaging and therapy.

4/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05682917 88111278 PMID: 3322784
Analysis of enteric neurons, glia and their interactions using explant cultures of the myenteric plexus.
Bannerman P G; Mirsky R; Jessen K R
Department of Anatomy and Embryology, University College, London, UK.
Developmental neuroscience (SWITZERLAND) **1987**, 9 (4) p201-27, ISSN 0378-5866 Journal Code: 7809375
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The enteric nervous system (ENS) of the gastrointestinal tract is the largest and most complicated division of the peripheral nervous system. The ENS possesses reflex pathways composed of motor neurons, interneurons and sensory neurons which act in an integrated fashion together with input from the central nervous system to control gut function. The neurons, morphologically and electrophysiologically a very heterogeneous group containing a large number of different proven and putative neurotransmitters, are intimately associated with enteric glia, which both at the morphological and molecular level resemble astrocytes. In this **review** we describe how explant cultures from the ENS have been used to investigate the neurochemical, molecular and electrophysiological characteristics of ENS neurons, the molecular properties of enteric glia and their interactions with one another.

4/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05582010 88000817 PMID: 2820514
Putative role of inositol phospholipid metabolism in neurons.
Sladeczek F
C.C.I.P.E., Montpellier, France.
Biochimie (FRANCE) Apr **1987**, 69 (4) p287-96, ISSN 0300-9084 Journal Code: 1264604
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed
Inositol phospholipids play a crucial role in the intracellular signal transduction in most cell types. Activation of an enzyme called phospholipase C or PIP2-phosphodiesterase (PIP2-PDE) leads to the production of two second messenger molecules, diacylglycerol (DG) and inositol 1,4,5-triphosphate (IP3). DG activates a kinase called protein kinase C, whereas IP3 mediates the release of Ca2+ from intracellular storage sites. The measurement of IP3 and its degradation products, inositol diphosphate (IP2) and inositol monophosphate (IP1) provides a way of assessing the extent to which this complex system has been activated. In the central nervous system (CNS) most of the studies on the neurotransmitter stimulated formation of inositol phosphates (IPs) have been performed on brain slices, a mixture of mainly neurons and **glial** cells. The recent development of pure neuronal cultures provides a means of determining which of these responses were of neuronal origin. The purpose of this **review** is to summarize the results obtained in neurons in primary **culture** together with a brief appraisal of the possible function of this second messenger system in neurons.

4/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05152193 86226363 PMID: 2423650
The generation and regeneration of oligodendroglia. A short **review**.

Debbage P L
Journal of the neurological sciences (NETHERLANDS) Feb **1986**, 72 (2-3) p319-36, ISSN 0022-510X Journal Code: 0375403
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
During postnatal development of the higher vertebrate CNS, large populations of oligodendroglia are generated from precursor cells in a very dependable way. In adult lesioned CNS tissues, local populations of oligodendroglia are replenished by proliferation of this replenishment varies from one species to another and also from one lesion type another. Studies on the developmental generation of oligodendroglia are reviewed here, delineating what is known of the early relationships between the CNS **glial** lineages and of what regulates this development. Contributions from recent cell biological work are considered against the background of morphological and radioautographic results. The quiescent condition of extremely slow turnover in the normal adult CNS is noted, and the dramatic effects of lesions on the neural cell environment are considered. Lesions can trigger proliferation at a much greater rate in the mature oligodendroglial population, as observed both in situ and in tissue **culture** ; in addition to persisting stem cells, the mature cells participate in replenishing the local oligodendroglial population. This regeneration from cells already committed to the oligodendroglial lineage may minimise such disturbing effects of the lesion environment as might distort replenishment of the population from precursor cells.

4/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05018326 86091780 PMID: 3001489
DNA content and chromosomal composition of malignant human gliomas.
Bigner S H; Bjerkvig R; Laerum O D
Neurologic clinics (UNITED STATES) Nov **1985**, 3 (4) p769-84, ISSN 0733-8619 Journal Code: 8219232
Document type: Journal Article; Review
Languages: ENGLISH

Main Citation Owner: NLM
Record type: Completed

A short **review** is given on DNA aberrations and chromosomal composition of malignant human gliomas. By flow cytometric DNA analysis, a wide range of different ploidies has been reported in biopsied gliomas, from diploid to strongly aneuploid nuclear DNA. However, with the preparation and analysis methods used so far, no clear relationship between the type of ploidy and histology or prognosis has been established. A high proportion of glioblastomas is near-diploid, indicating a high degree of biologic malignancy is not necessarily connected to aberration of the nuclear DNA content. It is possible that improved methods giving a higher degree of resolution will allow separation of the near-diploid populations of malignant human gliomas from normal diploid cells and permit the detection of subpopulations with small differences from the dominant DNA mode. Chromosomal studies of malignant gliomas have confirmed that the majority of them have near-diploid stemlines. These populations are seldom normal diploid, however, as both numerical and structural abnormalities are usually present. In addition, chromosomal analyses have shown that when gliomas are bimodal, the polyploid populations are usually doubled versions of the near-diploid ones. In contrast to the near-diploid populations that characterize biopsied malignant gliomas, both FCM studies and karyotyping have demonstrated that permanent cultured cell lines derived from malignant gliomas are usually near-triploid or near-tetraploid. Sequential karyotypic studies of these tumors from biopsy through establishment in vitro have shown an evolutionary pattern consisting of doubling of the original stemline, followed by gains or losses of individual chromosomes with new marker formation in late **culture**. Evaluation of biopsied malignant gliomas by karyotyping has also demonstrated that subgroups of them are characterized by specific numerical and structural deviations. These groupings may prove useful in predicting prognosis or responsiveness to specific therapeutic regimens. The specific chromosomal abnormalities observed in malignant human glioma may provide clues as to the genes important in **glial** transformation. As chromosomal loci for production of structural proteins and enzymes involved in **glial** metabolism are mapped and patterns of oncogene activation and amplification are determined for human gliomas, the meaning of the nonrandom chromosomal changes seen in these tumors may become clear.

4/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

04681309 85048705 PMID: 6388824
Invasiveness of primary brain tumors.
Laerum O D; Bjerkvig R; Steinsvag S K; de Ridder L
Cancer metastasis reviews (NETHERLANDS) **1984**, 3 (3) p223-36,
ISSN 0167-7659 Journal Code: 8302417
Document type: Journal Article; Review
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Primary malignant neoplasms of the nervous system differ from other types of malignancy in several ways. Clinical progression is due to local invasive growth, while metastases outside the skull are rare. The tumors show no sharp delimitation from the surrounding normal tissue. At the edge, an ill-defined area of invasive tumor cells, reacting **glial** cells and inflammatory cells is present. At the same time the primary brain tumors are biologically heterogeneous. In this **review**, a short survey of markers for malignancy in primary brain tumors is given, and some properties of importance for invasive behavior, are listed. These include different cellular enzymes, phagocytotic property, locomotive and proliferative characteristics. Studies of primary brain tumors in situ show invasive growth into the surrounding brain tissue, often followed by hemorrhage and necrosis. In addition spread of tumor cells takes place

along preexisting intracranial structures. Recently, several systems for the study of brain tumor invasiveness in **culture** have been elaborated. Both experimental and human gliomas have been tested. The target tissues include organ **culture** of embryonic chick heart muscle, chorioallantoic membrane, fetal rat brain tissue and reconstructed vessel walls. It has been shown that glioma cells are able to split junctions between normal cells. They destroy and phagocytose the normal cells and penetrate the normal tissue. The use of brain tissue and reaggregated brain cell cultures as target for glioma cells in **culture** opens the possibility for an elucidation of invasiveness as one of the most important properties of malignancy in the nervous system.

4/3,AB/24 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10791907 BIOSIS NO.: 199799413052
Ischemic disruption of glutamate homeostasis in brain: Quantitative immunocytochemical analyses.
AUTHOR: Ottersen Ole Petter(a); Laake Jon H; Reichelt Winfried; Haug Finn-Mogens; Torp Reidun
AUTHOR ADDRESS: (a)Dep. Anat., Inst. Basic Med. Sci., Univ. Oslo, PO Box 1105 Blindern, N-0317 Oslo**Norway
JOURNAL: Journal of Chemical Neuroanatomy 12 (1):p1-14 **1996**
ISSN: 0891-0618
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: More than 10 years ago, it was shown by microdialysis that the excitatory transmitter glutamate accumulates in the interstitial space of brain subjected to ischemic insult. This was one of the key observations leading to the formulation of the 'glutamate hypothesis' of ischemic cell death. It is now assumed that even a transient glutamate overflow may set in motion a number of events that ultimately cause cell loss in vulnerable neuronal populations. The aim of the present **review** is to discuss the intracellular changes that underlie the dysregulation of extracellular glutamate during and after ischemia, with emphasis on data obtained by postembedding, electron microscopic immunogold cytochemistry. While the time resolution of this approach is necessarily limited, it can reveal, quantitatively and at a high level of spatial resolution, how the intracellular pools of glutamate and metabolically related amino acids are perturbed during and after an ischemic insult. Moreover, this can be done in animals whose extracellular amino acid levels are monitored by microdialysis, allowing a direct correlation of extra- and intracellular changes. Immunogold analyses of brains subjected to ischemia have identified dendrites and neuronal somata as likely sources of glutamate efflux, probably mediated by reversal of glutamate uptake. The vesicular glutamate pool has been found to be largely unchanged after 20 min of ischemia. Ischemia causes an increased glutamate content and an increased glutamate/glutamine ratio in **glial** cells, as revealed by double immunogold labelling. This argues against the idea that **glial** cells contribute to the extracellular overflow of glutamate in the ischemic brain.

1996

4/3,AB/25 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09835733 BIOSIS NO.: 199598290651

Isolation, characterization, and use of stem cells from the CNS.
BOOK TITLE: Annual **Review** of Neuroscience
AUTHOR: Gage Fred H; Ray Jasodhara; Fisher Lisa J
BOOK AUTHOR/EDITOR: Cowan W M: Ed
AUTHOR ADDRESS: Dep. Neurosci., Sch. Med., Univ. Calif. San Diego, La Jolla, CA 92093-0627**USA
JOURNAL: Annual Review of Neuroscience 18p159-192 **1995**
BOOK PUBLISHER: Annual Reviews Inc., P.O. Box 10139, 4139 El Camino Way, Palo Alto, California 94306, USA
ISSN: 0147-006X ISBN: 0-8243-2418-8
DOCUMENT TYPE: Book; Literature Review
RECORD TYPE: Citation
LANGUAGE: English
1995

4/3,AB/26 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

08314186 BIOSIS NO.: 000094076509
REGULATION BY CHLORIDE ION OF ASTROGLIAL CELL FUNCTIONS AND MORPHOLOGICAL TRANSFORMATION
AUTHOR: BABA A
AUTHOR ADDRESS: DEP. PHARMACOL., FAC. PHARM. SCI., OSAKA UNIV., 1-6 YAMADA-OKA, SUITA, OSAKA 565, JAPAN.
JOURNAL: FOLIA PHARMACOL JPN 99 (5). 1992. 297-305. **1992**
FULL JOURNAL NAME: Folia Pharmacologica Japonica
CODEN: NYKZA
DOCUMENT TYPE: Review
RECORD TYPE: Abstract
LANGUAGE: JAPANESE

ABSTRACT: Recently, several lines of evidence have indicated the important roles of **glial** cells, especially astrocytes, in the regulation of neuronal functions. The neuro-glia interaction is one of the most important issues in neuroscience, including neuropharmacology. I received the present status and perspectives on the physiologic and pathologic functions of astrocytes in relation to the roles of intracellular Cl-. Astrocytes have diffferent types of Cl- transport systems, such as voltage-sensitive and ligand-gated channels; HCO3- -Cl- exchange; and Na+, K+, Cl- cotransport systems. Anion exchange and cotransport systems are responsible for intracellular pH regulation and astrocytic volume regulation, respectively. Especially, astrocytic volume regulation is physiologically important for reducing the concentrations of K+ and glutamate in the extracellular space by their uptake systems. Disturbance of astrocytic volume regulation is expressed as astrocytic swelling, which is usually observed in various brain pathologic states including ischemia. Experimentally, glutamate caused a typical swelling of astrocytes in **culture** by Cl- and Ca++-dependent processes. Glutamate-induced swelling is qualitatively different from reversible swelling induced by hypoosmotic medium. Recently, we found that Cl- is intracellular factor for modulating the receptor-adenylate cyclase system in brain slices. Similarly, the receptor- and forskolin-stimulated adenylate cyclase of astrocytes showed a clear Cl- dependence. This was functionally confirmed by astrocytic morphological transformation induced by the cyclic AMP system.

1992

4/3,AB/27 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07463145 BIOSIS NO.: 000040043294
NEW INSIGHTS INTO THE BIOLOGY OF NEURONS AND **GLIAL** CELLS IN TISSUE **CULTURE** IN-VITRO
AUTHOR: BAL-KLARA A; KALUZA J
AUTHOR ADDRESS: UL. SMETNA 12, 31-343 KRAKOW, POL.
JOURNAL: POSTEPY BIOL KOMORKI 17 (1). 1990. 71-82. **1990**
FULL JOURNAL NAME: Postepy Biologii Komorki
CODEN: PBKOD
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: POLISH
1990

4/3,AB/28 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06601396 BIOSIS NO.: 000087043558
DETECTION OF NEUROTERATOGENS WITH AN IN-VITRO CYTOTOXICITY ASSAY USING PRIMARY MONOLAYERS CULTURED FROM DISSOCIATED FETAL RAT BRAINS
AUTHOR: KHERA K S; WHALEN C
AUTHOR ADDRESS: SIR FREDERICK BANTING RES. CENT., NATL. HEALTH WELFARE, TUNNEY'S PASTURE, OTTAWA, ONT. K1A 0L2, CAN.
JOURNAL: TOXICOL IN VITRO 2 (4). 1988. 257-274. **1988**
FULL JOURNAL NAME: Toxicology In Vitro
CODEN: TIVIE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Brain tissues from 19-day-old Sprague-Dawley rat fetuses were trypsinized and then dissociated in a nutrient medium. The resulting cellular suspension was seeded in Falcon tissue-**culture** flasks and incubated at 37.degree. C in humidified air containing 5% CO2. The monocell layer obtained after incubation for 3 days consisted of two readily distinguishable cell types: neuronal cells with interconnecting neurites and fascicles, and non-neuronal or **glial**-type cells that were polygonal in appearance. The cell layers were exposed to graded concentrations of a test chemical dissolved in the nutrient medium. The cultures were examined daily for cell death and for inhibited outgrowth of neurites and fascicles for 3 days and the test was then terminated. Chemicals showing no cytotoxic effect at 2-mM concentration were generally not tested any further. Those found positive were tested at lower concentrations to determine the minimum cytotoxic concentration and the type of cell or cells affected. Of the 109 chemicals examined, 59 were non-cytotoxic at the 2-mM concentration or at the highest concentration at which they were soluble (1 mM for three compounds and 0.5 M for one), ten were preferentially cytocidal for non-neurons, 21 were selectively cytolethal for the neurons and ten were cytocidal for both neurons and non-neurons. The cytotoxicity of the remaining nine chemicals were regarded as unreliable because of the hyperosmolality of their solutions. The neuroteratogenic potential of a chemical, based on cytotoxicity data, was regarded as negligible if the cytocidal effect failed to occur in any cell type at a concentration of .gtoreq. 2 mM, or if the effect occurred only in non-neurons or in both neurons and non-neurons. The potential was considered positive if cellular degeneration at the lowest cytocidal concentration of a chemical occurred only in the neurons. The agreement between the neuroteratogenic potential in vivo, as reported in the literature, and the cytotoxicity data obtained in this study was very good for 82 chemicals, reasonable for ten, poor for four and undetermined for four. From the results of this investigation and a **review** of the published teratology data, the neuron and its precursor neuroepithelial cell appear as the most likely

initial targets for neuroteratogenic chemicals. Consequently, our in vitro system offers a promising approach for studies on neuroteratogens.

1988

4/3,AB/29 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06346039 BIOSIS NO.: 000036049192
TISSUE **CULTURE** OF RETINAL **GLIAL** CELLS
AUTHOR: SAVAGE F J; DAY J E; HOGG P; GRIERSON I
AUTHOR ADDRESS: DEP. PATHOL., INST. OPHTHALMOL., 17-25 CAYTON ST., LONDON EC1V 9AT.
JOURNAL: EYE (LOND) 2 (SUPPL.). 1988. S164-S179. **1988**
FULL JOURNAL NAME: EYE (London)
CODEN: EYEEE
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1988

4/3,AB/30 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05891871 BIOSIS NO.: 000034115020
NUTRIENTS AND HUMORAL SUBSTANCES IN THE MICROENVIRONMENT INFLUENCE THE DEVELOPMENT AND AGING OF **GLIAL** CELLS IN **CULTURE**
AUTHOR: VERNADAKIS A; SAKELLARIDIS N; MANGOURA D
AUTHOR ADDRESS: DEP. PSYCHIATRY, UNIV. COLO. SCH. MED., DENVER, COLO. 80262, USA.
JOURNAL: RASSIN, D. K., B. HABER AND B. DRUJAN (ED.). CURRENT TOPICS IN NUTRITION AND DISEASE, VOL. 16. BASIC AND CLINICAL ASPECTS OF NUTRITION AND BRAIN DEVELOPMENT; MEETING, CARACAS, VENEZUELA, DECEMBER 1985. IX+370P. ALAN R. LISS, INC.: NEW YORK, NEW YORK, USA. ILLUS. ISBN 0-8451-1615-0. 0 (0). 1987. 75-98. **1987**
CODEN: CTNDD
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1987

4/3,AB/31 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03074315 BIOSIS NO.: 000020017434
CHANGES IN BIOCHEMICAL PROPERTIES OF **GLIAL** CELLS IN **CULTURE** IN-VITRO DIFFERENTIATION
AUTHOR: VERNADAKIS A; PARKER K; NORENBERG M
AUTHOR ADDRESS: DEP. PSYCHIATRY, UNIV. COLO. SCH. MED., DENVER, COLO. 80262, USA.
JOURNAL: GIACOBINI, E., A. VERNADAKIS AND A. SHAHAR (ED.). TISSUE CULTURE IN NEUROBIOLOGY. XVIII+512P. RAVEN PRESS: NEW YORK, N.Y., USA. ILLUS. ISBN 0-89004-461-9. 0 (0). 1980. P411-426. **1980**
CODEN: 09048
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1980

4/3,AB/32 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

03074301 BIOSIS NO.: 000020017420
MOLECULAR MARKERS FOR THE ANALYSIS OF NEURAL DIFFERENTIATION IN **CULTURE**
AUTHOR: BIGNAMI A; KOZAK L P; DAHL D
AUTHOR ADDRESS: SPINAL CORD INJURY RES. LAB., HARV. MED. SCH., BOSTON. MASS. 02132, USA.
JOURNAL: GIACOBINI, E., A. VERNADAKIS AND A. SHAHAR (ED.). TISSUE CULTURE IN NEUROBIOLOGY. XVIII+512P. RAVEN PRESS: NEW YORK, N.Y., USA. ILLUS. ISBN 0-89004-461-9. 0 (0). 1980. P63-74. **1980**
CODEN: 09048
DOCUMENT TYPE: Review
RECORD TYPE: Citation
LANGUAGE: ENGLISH
1980
?

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Set     Items   Description
S1        844   GLIAL AND REVIEW AND PY<1999
S2          0   S1 AND BASAL AND CULTURE
S3         39   S1 AND CULTURE
S4         32   RD (unique items)
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          59464  GLIAL
         585806  REVIEW
        2544348  PY>1999
      S5    252  GLIAL AND REVIEW AND PY>1999
? s s5 and culture
            252  S5
         681293  CULTURE
      S6     18  S5 AND CULTURE
? rd
...completed examining records
      S7     13  RD (unique items)
? t s7/3,ab/all

 7/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13347358   22104412   PMID: 12109063
  Vector delivery methods and targeting strategies for gene therapy of
brain tumors.
  Rainov N G; Kramm C M
  Dept. Neurological Science, University of Liverpool, Clinical Sciences
Centre, Lower Lane, Liverpool L9 7LJ, United Kingdom. rainov@liv.ac.uk
  Curr Gene Ther (Netherlands) Nov 2001, 1 (4) p367-83, ISSN
1566-5232   Journal Code: 101125446
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  Efficient virus and non-virus vector systems for gene transfer to tumor
cells have been developed and tested in cell culture and in animal
experiments. With some of the earliest and most comprehensively evaluated
vectors, such as retroviruses, advanced clinical trials were performed in
tumor patients. Malignant primary brain tumors (gliomas) have been chosen
for the first clinical studies on novel gene therapy approaches because
these tumors are non-metastatic and develop on the largely postmitotic
background of normal glial and neuronal tissue. However, the human
cancer gene therapy studies performed so far were not as successful as
preclinical animal experiments. Furthermore, the clinical studies did not
address major limiting factors for in vivo gene therapy, such as
insufficient gene transfer rates to the tumor with the used local delivery
modalities, and the resulting inability of a particular transgene-prodrug
system to confer permanently eradicating cytotoxicity to the whole
neoplasm. Critical evaluation of gene transfer and therapy studies has led
to the conclusion that, even using identical vectors, the anatomical route
of vector administration can dramatically affect both the efficiency of
tumor transduction and its spatial distribution, as well as the extent of
intratumoral and intracerebral transgene expression. This review
concentrates on different physical methods for vector delivery to malignant
primary brain tumors in experimental or clinical settings: stereotactic or
direct intratumoral injection or convection-enhanced bulk-flow interstitial
delivery; intrathecal and intraventricular injection; and intravascular
infusion with or without modification of the blood-tumor-barrier. The
advantages and drawbacks of the different modes and delivery routes of in
vivo vector application, and the possibilities for tumor targeting by
modifications of the native tropism of virus vectors or by using
tissue-specific or inducible transgene expression are summarized.
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7/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13133935 21991235 PMID: 11996221
Sensor-based measurements of the role and interactions of free radicals in cellular systems.
McNeil Calum J; Manning Philip
Centre for Nanoscale Science and Technology, The Medical School, University of Newcastle upon Tyne, UK. calum.mcneil@ncl.ac.uk
Journal of biotechnology (Netherlands) Feb **2002**, 82 (4) p443-55, ISSN 0168-1656 Journal Code: 8411927
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Direct real-time electrochemical measurements have offered new insight into the importance of free radical interplay in a number of cell **culture** and in vivo models of neurodegenerative processes. This **review** highlights investigations carried out in this laboratory of real-time superoxide and nitric oxide free radical generation, and presents evidence of complex inter-relationships between these species. These include: a novel function for astrocytic nitric oxide synthase in controlling neuronal nitric oxide availability; and the demonstration that extracellular superoxide flux can lead to the generation of NO by **glial** cells. The possible consequences of these interactions are discussed.

7/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12903263 21683346 PMID: 11825297
Prospects for the treatment of Parkinson's disease using neurotrophic factors.
Barker R A; Hurelbrink C B
Addenbrooke's Hospital, Cambridge CB2 2PY, UK. rab46@cus.cam.ac.uk
Expert opinion on pharmacotherapy (England) Oct **2001**, 2 (10) p1531-43, ISSN 1465-6566 Journal Code: 100897346
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Parkinson's disease (PD) is a debilitating neurodegenerative condition that is characterised by a progressive loss of dopaminergic neurones of the substantia nigra pars compacta (SNpc) and the presence of alpha-synuclein cytoplasmic inclusions (Lewy bodies). Cardinal symptoms include tremor, bradykinesia, and rigidity, although cognitive and autonomic disturbances are not uncommon. Pharmacological treatment targeting the dopaminergic network is relatively effective at ameliorating these symptoms, especially in the early stages of the disease, but none of these therapies are curative and they generate their own problems. As dopaminergic neuronal death in PD occurs in a gradual manner, it is amenable to treatments that can either protect remaining dopaminergic neurones or prevent death of those neurones that have begun to die. Use of neurotrophic factors is a potential candidate, as various factors have been shown to increase dopaminergic neuronal survival in **culture** and promote survival and axonal growth in animal models of PD. **Glial** cell line-derived neurotrophic factor (GDNF) is currently the most effective substance that has been intensively studied and shown to have a specific 'dopaminotrophic' effect. This **review** will therefore focus on studies that have investigated GDNF and discuss the potential for neurotrophic factor treatment in PD.

7/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11287341 21330475 PMID: 11436356
NG2 cells in the brain: a novel **glial** cell population.
Nishiyama A
Department of Physiology & Neurobiology, University of Connecticut, USA. akiko.nishiyama@uconn.edu
Human cell : official journal of Human Cell Research Society (Japan) Mar **2001**, 14 (1) p77-82, ISSN 0914-7470 Journal Code: 8912329
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
There exists a significantly large population of **glial** cells in the mammalian central nervous system (CNS) that can be identified by the expression of the NG2 proteoglycan. Cells that express NG2 (NG2 cells) are found in the developing and mature CNS and are distinct from neurons, astrocytes, microglia, and mature oligodendrocytes. They are often referred to as oligodendrocyte progenitor cells because of their ability to differentiate into oligodendrocytes in **culture** . However, the observation that a large number of NG2 cells persist uniformly and ubiquitously in the adult CNS and display a differentiated morphology is not entirely consistent with the notion that NG2 cells are all oligodendrocyte progenitor cells. The role of NG2 cells in oligodendrocyte regeneration and their non-progenitor role in the mature CNS are discussed in this **review**.

7/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11250355 21255317 PMID: 11356147
Glycosaminoglycans in the study of mammalian organ development.
Davies J A; Fisher C E; Barnett M W
Department of Anatomy, University of Edinburgh Medical School, Teviot Place, Edinburgh EH8 9AG, U.K. Jamie.Davies@ed.ac.uk
Biochemical Society transactions (England) May **2001**, 29 (Pt 2) p166-71, ISSN 0300-5127 Journal Code: 7506897
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Glycosaminoglycans (GAGs) are linear polymers of amino sugar uronic acid disaccharides, and are generally attached to protein cores to form proteoglycans. GAGs interact with a large number of proteins and can participate in matrix organization, cell adhesion, differentiation, growth and apoptosis. Proteoglycans are expressed in tightly regulated spatio-temporal patterns during organ development, and changes in expression frequently correlate with developmental events. Here we **review** the evidence that GAGs play important roles in the development of mouse kidneys, which are organs that will undergo organotypic development in simple **culture** conditions and that are therefore highly accessible to experimentation. Depleting kidneys of GAGs, either biochemically or genetically, blocks the development of the urinary collecting-duct system, probably because critical signalling molecules require GAGs to form stable associations with their receptors. The insensitivity of GAG-deprived organ rudiments to physiological concentrations of growth factors can be used to screen candidate signalling molecules for morphoregulatory activity; candidate growth factors are applied at supraphysiological levels to GAG-deprived kidneys and assessed for their ability to rescue normal development. This approach has assisted the identification of four collecting-duct morphogens: hepatocyte growth

factor, **glial** cell line-derived neurotrophic factor, nerturin and persephin.

7/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11242893 21281584 PMID: 11388446
From stem cells towards neural layers: a lesson from re-aggregated embryonic retinal cells.
Layer P G; Rothermel A; Willbold E
Darmstadt University of Technology, Department of Developmental Biology and Neurogenetics, Germany.
Neuroreport (England) May 25 **2001**, 12 (7) pA39-46, ISSN 0959-4965 Journal Code: 9100935
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cells from dissociated embryonic avian retinae have the capacity to re-aggregate in rotation **culture** and form cellular spheres reconstituting a complete arrangement of all retinal layers. This exquisite phenomenon is based upon in vitro proliferation of multipotent precursor stem cells and spatial organization of their differentiating descendants. The addition of soluble factors from cultured retinal pigmented epithelial (RPE) or radial **glial** cells is essential to revert inside-out spheres (rosetted retinal spheres) into correctly laminated outside-out spheres (stratified spheres). Such complete restoration of a laminated brain tissue by cell re-aggregation has been achieved only for the embryonic avian retina, but not the mammalian retina, nor for other brain parts. This **review** summarises the history of the re-aggregation approach, presents avian retinal re-aggregate models, and analyses roles of the RPE and Muller cells for successful retinal tissue regeneration. It is predicted that these results will become biomedically relevant, as stem cell biology will soon open ways to produce large amounts of human retinal precursors.

7/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11232742 21263143 PMID: 11371004
Retinoic acid as a regulator of cytokine signaling after nerve injury.
Mey J
Institut fur Biologie II, RWTH Aachen, Germany. mey@bio2.rwth-aachen.de
Zeitschrift fur Naturforschung. C, Journal of biosciences (Germany) Mar-Apr **2001**, 56 (3-4) p163-76, ISSN 0341-0382 Journal Code: 8912155
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
After an injury of the central nervous system it is of foremost clinical concern to prevent nerve cell degeneration and to develop strategies for the support of axonal regeneration. This requires an understanding of traumatic processes in the nervous system and their regulation by intercellular cytokine signaling. Although injury-induced temporal changes in gene expression of many cytokines have been described in this context, much less is known about their regulation. This **review** proposes a role of retinoic acid (RA) as transcriptional regulator in nerve regeneration. Four lines of evidence support this hypothesis: (1) In various cell **culture** systems retinoids were found to interact with most cytokine signals that mediate cellular interactions after nerve lesions in vivo. (2) Necessary components of the retinoid signaling pathway

(aldehyde dehydrogenases, nuclear RA-receptors, cellular RA-binding proteins) are present in the adult nervous system, and **glial** cells produce RA in vitro. In addition, recent observations indicate that RA-synthesizing enzyme activity increases after nerve injury. (3) During development endogenous RA promotes **glial** and neuronal differentiation including the outgrowth of axons in the developing spinal cord, cerebellum, dorsal root ganglia and sympathetic ganglia. (4) Axonal regeneration of differentiated retinal ganglion cells and peripheral sensory neurons is enhanced by RA in vitro.

7/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10932148 20477493 PMID: 11026469
Excitatory amino acid neurotoxicity and modulation of glutamate receptor expression in organotypic brain slice cultures.
Zimmer J; Kristensen B W; Jakobsen B; Noraberg J
NeuroScreen, Ltd, Odense, Denmark. zimmer@imbmed.sdu.dk
Amino acids (AUSTRIA) **2000**, 19 (1) p7-21, ISSN 0939-4451
Journal Code: 9200312
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Using organotypic slice cultures of hippocampus and cortex-striatum from newborn to 7 day old rats, we are currently studying the excitotoxic effects of kainic acid (KA), AMPA and NMDA and the neuroprotective effects of glutamate receptor blockers, like NBQX. For detection and quantitation of the induced neurodegeneration, we have developed standardized protocols, including--a) densitometric measurements of the cellular uptake of propidium iodide (PI), --b) histological staining by Flouro-Jade, --c) lactate dehydrogenase (LDH) release to the **culture** medium, --d) immunostaining for microtubulin-associated protein 2, and --e) general and specific neuronal and **glial** cell stains. The results show good correlation between the different markers, and are in accordance with results obtained in vivo. Examples presented in this **review** will focus on the use of PI uptake to monitor the excitotoxic effects of --a) KA and AMPA (and NMDA) in hippocampal slice cultures, and --b) KA and AMPA in corticostriatal slice cocultures, with demonstration of differentiated neuroprotective effects of NBQX in relation to cortex and striatum and KA and AMPA. A second set of studies include modulation of hippocampal KA-induced excitotoxicity and KA-glutamate receptor subunit mRNA expression after long-term exposure to low, non-toxic doses of KA and NBQX. We conclude that organotypic brain slice cultures, combined with standardized procedures for quantitation of cell damage and receptor subunit changes is of great potential use for studies of excitotoxic, glutamate receptor-induced neuronal cell death, receptor modulation and related neuroprotection.

7/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10737335 20269526 PMID: 10811389
Neural stem cells: from cell biology to cell replacement.
Armstrong R J; Svendsen C N
Centre for Brain Repair, University of Cambridge, UK. rjea100@cam.ac.uk
Cell transplantation (UNITED STATES) Mar-Apr **2000**, 9 (2) p139-52, ISSN 0963-6897 Journal Code: 9208854
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

A large number of crippling neurological conditions result from the loss of certain cell populations from the nervous system through disease or injury, and these cells are not intrinsically replaced. Mounting evidence now suggests that replacement of depleted cell populations by transplantation may be of functional benefit in many such diseases. A diverse range of cell populations is vulnerable, and the loss of specific populations results in circumscribed deficits in different conditions. This diversity presents a considerable challenge if cell replacement therapy is to become widely applicable in the clinical domain, because each condition has specific requirements for the phenotype, developmental stage, and number of cells required. An ideal cell for universal application in cell replacement therapy would possess several key properties: it would be highly proliferative, allowing the ex vivo production of large numbers of cells from minimal donor material; it would also remain immature and phenotypically plastic such that it could differentiate into appropriate neural and **glial** cell types on, or prior to, transplantation. Critically, both proliferation and differentiation would be controllable. This **review** considers some of the evidence that stem cells exist in the central nervous system and that they may possess characteristics that make them ideal for broad application in cell replacement therapy.

7/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10701858 20225532 PMID: 10760549
Ion channels in **glial** cells.
Verkhratsky A; Steinhauser C
School of Biological Sciences, The University of Manchester, Oxford Road, Manchester, UK. alex.verkhratsky@man.ac.uk
Brain research. Brain research reviews (NETHERLANDS) Apr **2000**, 32 (2-3) p380-412, ISSN 0165-0173 Journal Code: 8908638
Document type: Journal Article; Review; Review, Academic
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Functional and molecular analysis of **glial** voltage- and ligand-gated ion channels underwent tremendous boost over the last 15 years. The traditional image of the **glial** cell as a passive, structural element of the nervous system was transformed into the concept of a plastic cell, capable of expressing a large variety of ion channels and neurotransmitter receptors. These molecules might enable **glial** cells to sense neuronal activity and to integrate it within **glial** networks, e.g., by means of spreading calcium waves. In this **review** we shall give a comprehensive summary of the main functional properties of ion channels and ionotropic receptors expressed by macroglial cells, i.e., by astrocytes, oligodendrocytes and Schwann cells. In particular we will discuss in detail **glial** sodium, potassium and anion channels, as well as glutamate, GABA and ATP activated ionotropic receptors. A majority of available data was obtained from primary cell **culture**, these results have been compared with corresponding studies that used acute tissue slices or freshly isolated cells. In view of these data, an active **glial** participation in information processing seems increasingly likely and a physiological role for some of the **glial** channels and receptors is gradually emerging.

7/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10582790 20121681 PMID: 10658180
The oligodendroglia cytoskeleton in health and disease.
Richter-Landsberg C
Department of Biology, Molecular Neurobiology, University of Oldenburg,

Germany. Christiane.Richter.Landsberg@UNI-Oldenburg.DE
Journal of neuroscience research (UNITED STATES) Jan 1 **2000**, 59 (1) p11-8, ISSN 0360-4012 Journal Code: 7600111
Document type: Journal Article; Review; Review, Tutorial
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Oligodendrocytes have a high rate of synthetic activity and produce vast amounts of myelin. The membrane production requires specific sorting and transport processes and structural support. In **culture**, oligodendrocytes extend flat membranous sheets containing an extensive cytoskeletal network of microtubules (MTs) and microfilaments (MFs). The microtubules participate in the elaboration and stabilization of the myelin-containing cellular processes and have an impact not only on the complex oligodendroglia architecture but also influence their functions. They participate in intracellular sorting processes and the translocation of myelin basic protein (MBP) mRNAs to the forming myelin sheath. The two major groups of neuronal microtubule-associated proteins (MAPs), MAP2 and tau are expressed in oligodendrocytes and might be involved in the regulation of MT stability and organization. Myelin-specific proteins, such as MBP and 2',3'-cyclic nucleotide 3'-phosphohydrolase (CNP), interact with the cytoskeleton. **Glial** changes occur in a variety of neurodegenerative diseases, and **glial** fibrillary tangles and **glial** cytoplasmic inclusions (GCIs), containing abnormal microtubular structures which stain positively for stress proteins and microtubule-associated proteins, are found in oligodendrocytes of the affected brains. The role of MTs and their associated proteins in oligodendrocytes during normal development and pathological situations is specifically emphasized in this **review**.

7/3,AB/12 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13642731 BIOSIS NO.: 200200271552
The astrocyte/meningeal cell interface: A barrier to successful nerve regeneration?
AUTHOR: Shearer Morven C(a); Fawcett James W
AUTHOR ADDRESS: (a)Department of Physiology, University of Cambridge, Cambridge, CB2 3EG**UK E-Mail: mcs36@cam.ac.uk
JOURNAL: Cell & Tissue Research 305 (2):p267-273 August, **2001**
MEDIUM: print
ISSN: 0302-766X
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Following injuries to the adult mammalian CNS meningeal cells migrate into the lesion cavity, forming a fibrotic scar and accessory glia limitans. This infiltration re-establishes the meningeal layer that normally surrounds the CNS, and so reforms the barrier between the CNS and external environment, thus protecting the damaged region from events outside it. However, the newly formed meningeal layer and glia limitans may impede subsequent nerve regeneration through the injured region. This structure can be modelled in vitro using an astrocyte/meningeal co-**culture** system. We have examined patterns of neurite outgrowth on such cultures, and we find that axons cross readily from meningeal cells to astrocytes, but are unwilling to cross in the other direction. The distribution of cell surface and matrix molecules on these cultures is described, and the effect of various pharmacological interventions which can affect axon growth between the two cell types is summarised in this **review**.

2001

7/3,AB/13 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13628283 BIOSIS NO.: 200200257104
Expression and regulation of apolipoprotein E receptors in the cells of the central nervous system in **culture**: A **review**.
AUTHOR: Fan Qi-Wen; Iosbe Ichiro; Asou Hiroaki; Yanagisawa Katsuhiko; Michikawa Makoto(a)
AUTHOR ADDRESS: (a)Department of Dementia Research, National Institute for Longevity Sciences, 36-3 Gengo, Morioka, Obu, Aichi, 474-8522**Japan
E-Mail: michi@nils.go.jp
JOURNAL: Journal of the American Aging Association 24 (1):p1-10 January, **2001**
MEDIUM: print
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The importance of apolipoprotein E (apoE) in the central nervous system (CNS) became increasingly clear since the descovery that apoE epsilon4 allele is a major risk factor for Alzheimer's disease. ApoE is one of the major apolipoproteins that acts as a ligand for the cellular uptake of lipoproteins via apoE receptors, members of low-density lipoprotein receptor (LDLR) family, in the CNS. Recently, LDLR family has been shown to have new functions that modulate intracellular signalling and affect neuronal and **glial** functions, survival and regeneration. However, the pattern of expression of apoE receptors in the CNS has not been fully clarified yet. The LDLR, very low density lipoprotein receptor (VLDLR), LDLR-related protein (LRP), and apolipoprotein E receptor 2 (apoER2) are known to bind to and internalize apoE-containing lipoproteins. Here we summarize the expression of apoE receptors in the CNS and demonstrate additional our original data on cell type specific expression and regulation of those receptors in the CNS, using in situ hybridization and RT-PCR. The cells used in our study were highly enriched cultures of neurons, astrocytes, microglia and oligodendrocytes isolated from rat brain and neuroblastoma cell line, Neuro2a. All of these four types of receptors were shown to be expressed in neurons, astrocytes, microglia and oligodendrocytes, while LDLR and LRP were expressed in Neuro2a cells. We further examined the regulation of the expression of these receptors by altering the cholesterol content of the cells, and found that only the LDLR expression was downregulated following internalization of lipoprotein cholesterol and upregulated by cholesterol deprivation, in neuronal and astroglial cells. These data together with previous studies suggest that LDLR, VLDL, LRP, and apoER2 may be involved in apoE-mediated lipid uptake and/or intracellualr signalling in the cells of the CNS cells, i.e., neurons, astrocytes, microglia, and oligodendrocytes.

2001

nestin. After 4 weeks in **culture**, a subset of GFAP-positive cells emerged that no longer costained with nestin. These results describe nestin expression not only in CNS **progenitor** cells but also in the cells which were in transition from a **progenitor** stage to **glial** differentiation. Collectively, these data suggest a differential temporal regulation of nestin expression during **glial** and neuronal **cell** differentiation. Copyright 2000 Academic Press.

16/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10607430 20145991 PMID: 10679766
Developmental changes in **neural progenitor cell** lineage commitment do not depend on epidermal growth factor receptor signaling.
Zhu G; Mehler M F; Mabie P C; Kessler J A
Departments of Neurology and Neuroscience, Albert Einstein College of Medicine, Bronx, New York 10461, USA.
Journal of neuroscience research (UNITED STATES) Feb 1 **2000**, 59 (3) p312-20, ISSN 0360-4012 Journal Code: 7600111
Contract/Grant No.: NS20013; NS; NINDS; NS20778; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Multipotent **neural progenitor** cells become progressively more biased towards a **glial** fate during development coincident with an increase in expression of the epidermal growth factor receptor (EGFR). To determine whether differences in lineage commitment of **neural progenitor** cells from different stages are causally related to expression of the EGFR and whether generation of glia is EGFR-dependent, we used an EGFR-specific tyrosine kinase inhibitor, PD158780, to block the activation of EGFR in **progenitor** cells. Treatment of cultured neonatal **progenitor** cells with PD158780 completely blocked EGF-induced proliferation of the cells but did not affect bFGF-induced proliferation. Nevertheless, treatment with the inhibitor failed to inhibit the generation of astroglia in the presence of either EGF or bFGF. Treatment with bone morphogenetic protein-2 (BMP2) enhanced astroglial differentiation and suppressed oligodendroglial (OL) differentiation. PD158780 treatment had no effect on the BMP2-induced astroglial differentiation or OL suppression. These observations suggest that the generation of astroglia is not dependent on EGFR activation. Because it was still possible that the **progenitor cell** responses reflected a prior history of EGFR signaling, rat forebrain cells were cultured in the presence of PD158780 from a time (E12.5) preceding expression of the EGFR. After time in **culture** , the E12.5 cells expressed EGFR by Western analysis both in the presence and in the absence of PD158780, but activation of EGFR kinase (receptor autophosphorylation) was undetectable in the presence of PD158780 and the cells did not proliferate in response to EGF. Nevertheless, astroglial differentiation was normal in PD158780-treated cells both in the absence and in the presence of BMPs or CNTF. Furthermore, the propensity towards **glial** differentiation increased with time in **culture** even in the absence of EGFR signaling. This suggests that the increased bias towards **glial** differentiation during development does not depend on EGFR signaling. Copyright 2000 Wiley-Liss, Inc.

16/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10591624 20127727 PMID: 10665961
Transformation by radiation of rat foetal **glial** cells.
Peyre H M; Coffigny H; Reillaudou M; Beaumatin J; Morin M; Luccioni C

CEA/DSV/DRR, Laboratoire de Radiobiologie Cellulaire (LRCE), Fontenay aux Roses, France.
International journal of radiation biology (ENGLAND) Jan **2000**, 76 (1) p87-94, ISSN 0955-3002 Journal Code: 8809243
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: To establish and characterize an in vitro model of radiation-induced transformation of normal **glial** cells. MATERIALS AND METHODS: During the last week of gestation, pregnant Sprague-Dawley rats were either irradiated at 3.5 Gy (0.022 Gy h(-1)) with a 60Co source or sham irradiated. On day 21 of gestation, cortical **nerve** cells from foetuses were isolated, and then maintained in **culture** for about 100 passages, in presence of 10(-9) g/ml of tetradecanoyl phorbol acetate (TPA). To follow transformation, various parameters: **cell** type, proliferation, clonogenicity, karyotypes and tumorigenicity, were studied at different passages. RESULTS: As the number of passages increased, control cells lost their **glial** morphology and were immortalized. They kept on expressing specific markers of type 2 astrocytes (**glial** fibrillary acid protein (GFAP) and A2B5). Karyotypes remained near diploid. At all passages tested, they were not tumorigenic in nude mice. Irradiated cells expressed the 2A **progenitor cell** specific markers: GFAP, vimentin and A2B5. Karyotypes evolved toward polyploidy and cells displayed an iso 7 and a marker. These changes were synchronous with modifications in tumorigenicity. Metastases were even observed in nude mice. CONCLUSIONS: Cells from irradiated animals were fully transformed, while cells from sham irradiated animals were only immortalized.

16/3,AB/24 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13619426 BIOSIS NO.: 200200248247
Identification of genes in the oligodendrocyte lineage through the analysis of conditionally immortalized **cell** lines.
AUTHOR: Campagnoni Celia W; Landry Charles F; Pribyl Thomas M; Schonmann Vilma; Kampf Kathy; Handley Vance W; Watson Joseph B; Bongarzone Ernesto R; Campagnoni Anthony T(a)
AUTHOR ADDRESS: (a)UCLA Medical School, Neuropsychiatric Institute, 760 Westwood Plaza, Room 47-448, Los Angeles, CA, 90024-1759**USA E-Mail: acampagnoni@mednet.ucla.edu
JOURNAL: Developmental Neuroscience 23 (6):p452-463 November-December, **2001**
MEDIUM: print
ISSN: 0378-5866
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The mouse oligodendrocyte **cell** lines, N19 and N20.1, were used as sources of potential stage-specific RNA in order to construct a subtraction library enriched in cDNAs expressed early in the oligodendrocyte (OL) lineage. From this library, 23 clones were examined and three were examined in most detail. The mRNAs of the three library clones were preferentially expressed in the N19 (**progenitor**) compared to the N20.1 (immature) OL line. One of these corresponded to the intermediate filament protein cytokeratin K19, which has not been reported to be expressed in OLs previously. Another was identified as the mouse homolog of T-cadherin, previously reported not to be present in OLs. Antisera raised against a T-cadherin peptide indicated the protein colocalized with the OL lineage markers A2B5, A007, and 01 in mouse primary **glial** cultures. However, small round cells resembling OL

precursors labeled intensely with T-cadherin, but were negative for the other markers, suggesting that this gene might be expressed earlier in the lineage. In early postnatal brain, in addition to the expected neuronal tracts, the T-cadherin antibody labeled small bipolar cells, apprx8-10 mum in diameter, in white matter tracts. These cells had the morphology of OLs or their precursors and were identified within the cerebellar white matter and the corpus callosum, regions rich in OLs. The third clone, 3g5, was homologous to the P8 clone isolated from rat pancreas. It encoded an 80-amino-acid polypeptide with a protein kinase C domain suggesting a possible role in signal transduction. Antisera to this peptide also colocalized 3g5 with cells expressing A2B5, A007, and 01 in **culture** and in cells within white matter tracts which had the same morphology as those labeled by T-cadherin in these regions. In addition to these, beta10 thymosin and mevalonate kinase clones were also isolated from the screen.

2001

16/3,AB/25 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13581379 BIOSIS NO.: 200200210200
Adult rodent neurogenic regions: The ventricular subependyma contains **neural** stem cells, but the dentate gyrus contains restricted progenitors.
AUTHOR: Seaberg Raewyn M(a); van der Kooy Derek
AUTHOR ADDRESS: (a)University of Toronto, 8 Taddle Creek Road, Room 1105, Medical Sciences Building, Toronto, Ontario, M5S 1A8**Canada E-Mail: raewyn.seaberg@utoronto.ca
JOURNAL: Journal of Neuroscience 22 (5):p1784-1793 March 1, **2002**
MEDIUM: print
ISSN: 0270-6474
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Neurogenesis persists in two adult brain regions: the ventricular subependyma and the subgranular **cell** layer in the hippocampal dentate gyrus (DG). Previous work in many laboratories has shown explicitly that multipotential, self-renewing stem cells in the subependyma are the source of newly generated migrating neurons that traverse the rostral migratory stream and incorporate into the olfactory bulb as interneurons. These stem cells have been specifically isolated from the subependyma, and their properties of self-renewal and multipotentiality have been demonstrated in vitro. In contrast, it is a widely held assumption that the "hippocampal" stem cells that can be isolated in vitro from adult hippocampus reside in the neurogenic subgranular layer and represent the source of new granule **cell** neurons, but this has never been tested directly. Primary **cell** isolates derived from the precise microdissection of adult rodent neurogenic regions were compared using two very different commonly used **culture** methods: a clonal colony-forming (neurosphere) assay and a monolayer **culture** system. Importantly, both of these **culture** methods generated the same conclusion: stem cells can be isolated from hippocampus-adjacent regions of subependyma, but the adult DG proper does not contain a population of resident **neural** stem cells. Indeed, although the lateral ventricle and other ventricular subependymal regions directly adjacent to the hippocampus contain **neural** stem cells that exhibit long-term self-renewal and multipotentiality, separate neuronal and **glial** progenitors with limited self-renewal capacity are present in the adult DG, suggesting that neuron-specific progenitors and not multipotential stem cells are the source of newly generated DG

neurons throughout adulthood.
2002

16/3,AB/26 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13523049 BIOSIS NO.: 200200151870
Analysis of expression of adhesion molecules by cord blood derived multipotent **progenitor** cells after **culture** with osteogenic and neurogenic differentiation signals.
AUTHOR: Wall Donna A(a); Quinn Cheryl O(a); Goodwin Holly S(a)
AUTHOR ADDRESS: (a)Pediatrics, Saint Louis University, Saint Louis, MO**USA
JOURNAL: Blood 98 (11 Part 2):p125b-126b November 16, **2001**
MEDIUM: print
CONFERENCE/MEETING: 43rd Annual Meeting of the American Society of Hematology, Part 2 Orlando, Florida, USA December 07-11, 2001
ISSN: 0006-4971
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Similar to bone marrow, umbilical cord blood (UCB) contains a small population of nonhematopoietic cells that have the capacity to be expanded and cultured long term. These adherent fibroblastoid cells, when exposed to appropriate secondary signals, will express phenotypic features of bone (expression of alkaline phosphatase, hydroxyapatite nodules, calcium flux), fat (neutral lipid vacuoles), **neural** (expression of (BETA)-tubulin III and **glial** fibrillary acidic protein), and stromal cells. We have termed this population multilineage **progenitor** cells (MPC). Compared to BM derived cells, UCB MPC under our standard **culture** conditions stained less intensely with antibodies to the adhesion molecules CD105(SH2) and CD166(ALCAM), which are defining markers of this population. Combined with the observation that UCB MPC cultures took longer to establish, we postulated that UCB MPC might represent a more primitive population compared to the MPC grown from BM. We examined the effect of **culture** in differentiation media on UCB MPC adhesion molecule expression, potentially as a measure of maturation. UCB was collected in CPD, ficolled and plated at a concentration of 1X106MNCs/cm2 in low glucose DMEM with 10% FBS. Media was changed at 24 hours and then weekly with a 50% exchange. Cells were incubated at 37degreeC in at least 5% CO2 for at least 6 weeks. After 3-4 weeks, colonies of adherent fibroblastoid cells were apparent in the flasks. Once 50-60% confluent, cells were passaged by trypsinization and replated in the **culture** media. After the second passage these cells had no hematopoietic potential or expression of hematopoietic antigens. These cells were positive for CD13, CD29, CD44, and were dimly positive for CD105 and CD166. UCB MPCs described above were then cultured in the presence of osteogenic differentiation factors ((BETA)-glycerol phosphate, ascorbic acid and dexamethasone) or in the presence of neurogenic differentiation factors (EGF and bFGF). The cells were exposed to differentiation media for seven days and then analyzed by flow cytometry for changes in adhesion antigen expression. With the addition of osteogenic growth factors, adhesion molecule expression by UCB MPC became similar to that of unstimulated BM MPC. Interestingly, BM MPC frequently had a spontaneous expression of bone phenotypic features. UCB MPC after **culture** with neurogenic growth factors concomitantly expressed neuro-specific antigens ((BETA)-tubulin III and GFAP), however did not result a change in adhesion molecule expression. The nature of the MPC population is still poorly understood - distinct **cell** population vs artifact of **culture**. However the MPC population that is grown from UCB has distinct differences from that isolated from BM. Under osteogenic **culture** conditions the UCB adhesion molecule expression becomes similar to that of unstimulated BM. Studies at the

clonal level are needed to demonstrate if the **cell** population isolated from cord blood is in fact a true **cell** population and whether UCB MPC are more primitive than those isolated from BM.

2001

16/3,AB/27 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13375091 BIOSIS NO.: 200200003912
PSA-NCAM modulates PDGF-induced chemotaxis of O-2A **glial progenitor** cells.
AUTHOR: Zang H(a); Calaora V(a); Vutskits L(a); Rougon G; Kiss J Z(a)
AUTHOR ADDRESS: (a)Morphology, University of Geneva Med. Sch, Geneva 4** Switzerland
JOURNAL: Society for Neuroscience Abstracts 27 (2):p2376 **2001**
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To investigate the role of PSA-NCAM in O-2A **cell** migration, astroglial monolayers were wounded by scratching that produced a 560 um wide denuded area. We observed that the wound site was progressively repopulated by migrating O-2A cells. Treatment of lesioned cultures with Endo-N that specifically removes PSA from cells, reduced migration into the denuded area and completely blocked the wound closure. Video-time lapse analysis showed that in the presence of Endo N, O-2A cells remained motile, but did not move away from the monolayer. Inclusion to the **culture** medium of PDGF (10ng/ml), that is known to increase the migration of O-2A cells, reversed the effect of Endo N. In addition, the migration of O-2A cells was blocked in the presence of an anti PDGF antibody. These results indicate that endogenous PDGF is required for the migration of O-2A cells and PSA-NCAM may modulate the responsiveness of these cells to this growth factor. To test this hypothesis, we isolated and purified O-2A cells using Percoll gradient centrifugation and analyzed directional migration (chemotaxis) and random migration (chemokinesis) of cells using a microchemotaxis chamber. We observed that PDGF stimulated O-2A migration in a dose dependent manner. In the presence of Endo N or an anti PSA antibody, chemotaxis but not chemokinesis was significantly reduced. On the other hand, Endo N did not influence the chemotaxis of O-2A **cell** to bFGF. These results demonstrate that the PSA chain on NCAM is not required for random migration of O-2A cells but it could modify directional migration of these cells in response to PDGF.

2001

16/3,AB/28 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13355389 BIOSIS NO.: 200100562538
Beta-catenin mediates effects of FGF2 in promoting neuronal lineage commitment by multipotent **progenitor** cells.
AUTHOR: Fu W(a); Kessler J(a)
AUTHOR ADDRESS: (a)Dept Neurol, Northwestern Univ Sch Med, Chicago, IL**USA
JOURNAL: Society for Neuroscience Abstracts 27 (2):p1815 **2001**
MEDIUM: print

CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience
San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Commitment of cortical multipotent stem cells to neuronal and **glial** lineages in vitro is influenced by the concentration of FGF2 to which they are exposed. To examine mechanisms underlying the effects of FGF2, E12 mouse ventricular zone (VZ) cells were treated with different concentrations of FGF2 (10 ng/ml and 50 ng/ml), and expression of 9000 genes was examined by microarray analysis at 6 hours and 24 hours after FGF2 treatments. Surprisingly FGF2 treatment increased levels of beta-catenin mRNA by as much as 31-fold. To investigate the role of beta-catenin in differentiation of multipotent cells, we generated four expression constructs of beta-catenin including full length, N-terminal truncated, C-terminal truncated, and both N and C-terminal truncated beta-catenin, and delivered the constructs into P19 cells (a multipotent stem **cell** line). All of the full length and truncated beta-catenin proteins promoted differentiation of P19 cells into neurons. Moreover, these findings were replicated in E13 VZ cells in **culture** using retroviral transduction of the full length and truncated beta-catenin constructs. Our observations suggest that FGF2 may regulate stem **cell** differentiation via activation of the beta-catenin pathway. Further, only the middle interaction domain of beta-catenin protein is required to promote neuronal lineage commitment by stem cells. How neuronal lineage commitment is regulated by beta-catenin interactions with other known and unknown proteins is under investigation.

2001

16/3,AB/29 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13340041 BIOSIS NO.: 200100547190
CD9 expression start from late stage of oligodendrocyte **progenitor** cells.
AUTHOR: Terada N(a); Baracskay K; Melrose S; Brophy P J; Trapp B D(a)
AUTHOR ADDRESS: (a)Neurosciences, Cleveland Clinic Foundation, Cleveland, OH**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1):p1238 **2001**
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience
San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: CD9, a tetraspanin superfamily member, has been detected in CNS myelin. In this study, the timing of the appearance of CD9 was examined in postnatal rat brain. Sections from neonatal rat brain were double labeled for CD9 and markers specific for oligodendrocyte **progenitor** cells (NG2 proteoglycan), astrocytes (GFAP) and microglia (macrophage regulatory factor-1). Some overlap between CD9 and NG2 positive oligodendrocyte **progenitor** cells was detected. CD9 was not detected in astrocytes and microglia. CD9 was expressed by premyelinating oligodendrocytes in vivo. As in vivo, CD9 was expressed in some NG2 positive **progenitor** cells and in oligodendrocytes in mixed **glial culture** from postnatal rat brain. These data suggest that CD9 is first expressed in the late oligodendrocyte **progenitor**

stage in vivo and in vitro. CD9 is known to associate with integrins and other tetraspanin superfamily proteins. Immunoprecipitation of CD9 from postnatal rat cerebrum identified coprecipitated Tspan-2, a tetraspanin protein recently identified in oligodendrocytes. Following **cell** surface biotin labeling of postnatal rat cerebrum, a 64kD protein was immunoprecipitated with CD9 antibody. CD9-associating molecular complex may function to promote oligodendrocyte differentiation from **progenitor** cells to myelinating oligodendrocytes.

2001

16/3,AB/30 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13312827 BIOSIS NO.: 200100519976
Adult **neural progenitor** cells survive transplantation into the acutely injured spinal cord.
AUTHOR: Vroemen M(a); Winkler J(a); Weidner N(a)
AUTHOR ADDRESS: (a)Neurology, University of Regensburg, Regensburg**Germany
JOURNAL: Society for Neuroscience Abstracts 27 (1):p967 **2001**
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Adult **neural progenitor** cells (NPC) represent promising cells to replace the disrupted **glial** cytoarchitecture as a prerequisite for long-distance axon regeneration following spinal cord injury (SCI). NPC have been shown to survive after transplantation into the intact and subacutely injured spinal cord, and to differentiate into **glial** cells. In the present study, we examined the survival and differentiation pattern of adult NPC grafted into the acutely injured spinal cord. Fibroblast growth factor 2 (FGF2) responsive NPC were isolated from adult rat spinal cord and propagated in vitro. After induction of differentiation in **culture**, cells maintained over multiple passages expressed markers for astrocytes, oligodendrocytes and neurons. NPC were either transduced in vitro to express green fluorescent protein (GFP) or pre-labeled with BrdU. Adult rats received dorsal funiculus transections followed immediately by transplantation of NPC as neurospheres into the lesion cavity (n=9), animals with lesions only served as controls (n=6). Three weeks post-op, grafted NPC identified by GFP expression or BrdU-labeling integrated and migrated in the acutely injured spinal cord. Grafted cells differentiated into **glial**, but not into neuronal lineages. There was no difference in the lesion cavity size between grafted and non-grafted animals. These results demonstrate that adult NPC survive transplantation into the acutely injured spinal cord and can be transduced to express GFP in vivo, however, NPC grafts were not able to fill cystic lesion cavities.

2001

16/3,AB/31 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13302222 BIOSIS NO.: 200100509371
Multipotential (stem) cells isolated from human umbilical cord blood express both neuronal and **glial** markers and engraft after

transplantation in the rat.
AUTHOR: Bicknese A R(a); Henderson V C(a)
AUTHOR ADDRESS: (a)Neurology, Saint Louis University, Saint Louis, MO**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1):p632 **2001**
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Cells that demonstrate self-renewal and multipotentiality are called **progenitor** cells or stem cells and have been recently discovered not only during early embryogenesis, but also in the differentiated tissues of mature bone marrow and brain. We have isolated a similar population of CD45 negative cells from umbilical cord blood that behave as multi-lineage **progenitor** cells and can be greatly expanded in tissue **culture**. Exposure to fibroblast growth factor (bFGF) and human epidermal growth factor (bFGF) induces expression of neuronal and **glial** markers. Western immunoblots demonstrate expression of both beta-tubulin III and **glial** fibrillary acidic protein (GFAP). Immunocytochemistry of the cells showed intense labeling to both compounds on the intracellular cytoskeleton. Many cells are double labeled, showing dual expression of both neuronal and **glial** markers. Cells transplanted into the sub-dural space or ventricular system of neonatal rats will engraft within the brain parenchyma, meninges and choroid plexus. Umbilical cord-derived **progenitor** cells are a renewable, inexhaustible resource obtained from umbilical cord blood that would otherwise be discarded after delivery. Human-derived multipotent cells hold out great hope as vehicles for gene therapy or for cellular therapeutics for the treatment of neurodegenerative disease.

2001

16/3,AB/32 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13279778 BIOSIS NO.: 200100486927
Effects of neurotrophic factors on low density cortical cultures.
AUTHOR: Shacka J J(a); Beckman J S(a); Estevez A G
AUTHOR ADDRESS: (a)Physiology and Biophysics, Univ. Alabama at Birmingham, Birmingham, AL**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1):p357 **2001**
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recent studies suggest that the same neuotrophin can elicit both protective and toxic effects in primary neuronal **culture**, which may depend not only on the **culture** conditions but also the presence or absence of Tyrosine kinase neurotrophin (Trk) and p75 receptors. We are testing whether the effects of neurotrophins are receptor-specific and involve mechanisms of oxidative stress in low-density cortical cultures. Dissociated E18 rat cortical cells were plated at 50 cells/sq. mm in Neurobasal media containing B-27 supplement on a polyornithine substrate. Immunofluorescence studies indicate that >95% of all cells are

neurofilament positive and <5% are astrocytes. Brain derived neurotrophic factor (BDNF), **glial cell** line-derived neurotrophic factor (GDNF), **nerve** growth factor (NGF), neurotrophin (NT)3 and NT4 were added (0.1 to 10,000 pg/ml) immediately after plating and on days 4 (D4) and D11 in vitro (IV). Viable cells were counted on D1, 4, 7 and 14 IV. Without trophic factors, survival decreased steadily over time, reaching a low of apprx40% on D14IV in comparison to D1IV. Upon treatment with 10,000 pg/ml BDNF, GDNF and NT4, survival approached 100% on D14IV in comparison to D1IV, while survival with NGF was similar to that of control. Additionally, treatment with 10,000 pg/ml GDNF induced the expression of astrocytes on D14IV. Several potential explanations for these data will be discussed, including neurotrophin-induced, receptor-specific **cell** death, proliferation of **progenitor** cells, and the role of nitric oxide synthase in neuronal death.

2001

16/3,AB/33 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13279436 BIOSIS NO.: 200100486585
Identification and isolation of multipotential **neural** **progenitor** cells from the adult human white matter.
AUTHOR: Nunes M(a); Roy N(a); McKhann G; Goldman S A
AUTHOR ADDRESS: (a)Neurology, Cornell U. Med. College, New York, NY**USA
JOURNAL: Society for Neuroscience Abstracts 27 (1):p56 **2001**
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience San Diego, California, USA November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Oligodendrocytic **progenitor** cells (OPCs) of the adult human white matter (AHWM) may be recognized by their transcriptional activation of the CNP2 promoter, and isolated by FACS after transfection with P/CNP2-regulated hGFP. OPCs also express the early **neural** marker recognized by MAb A2B5, by which they may also be extracted from adult brain by FACS. They are mitotic, and in high-density **culture** give rise to oligodendrocytes, and less so to astrocytes. Though nominally **glial**, P/CNP2:hGFP+ OPCs sorted from AHWM may also generate occasional neurons, especially in low density **culture**. We thus asked whether the OPC of the AHWM might be a type of multipotential **neural progenitor cell**. We report here that **progenitor** cells derived from the AHWM can rapidly expand as self-renewing and multipotential clones, which indeed generate neurons as well as glia. Limiting dilution with repetitive passage and clonal expansion as neurospheres, in tandem with retro-viral lineage analysis, revealed that these cells were able to both self-renew and co-generate neurons and glia in vitro. In addition, xenograft to E17 forebrain vesicles revealed that these cells were able to give rise to all major **neural** phenotypes in vivo. Thus, the **progenitor cell** of the AHWM might be predisposed to give rise to oligodendrocytes by virtue of both its neighbors and its environment, but may also give rise to neurons once removed from local instructive signals. These data argue that a distinct pool of mitotically-competent, self-renewing **neural** stem cells resides in the adult human white matter.

2001

16/3,AB/34 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13203319 BIOSIS NO.: 200100410468
Analysis of fractal dimension of O2A **glial** cells differentiating in vitro.
AUTHOR: Behar Toby N(a)
AUTHOR ADDRESS: (a)36 Convent Drive, Building 36, Room 2C02, Bethesda, MD, 20892-4066: Toby@codon.nih.gov**USA
JOURNAL: Methods (Orlando) 24 (4):p331-339 August, **2001**
MEDIUM: print
ISSN: 1046-2023
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Fractal dimension is a quantitative measure of morphological complexity. **Glial** cells of the oligodendrocyte-type 2 astrocyte (O2A) lineage exhibit increasing morphological complexity as they differentiate in vitro. Enriched populations of O2A **progenitor** cells isolated from neonatal rat cerebral hemispheres or optic nerves were allowed to differentiate in vitro, and their fractal dimensions were measured over time. The fractal dimensions of the maturing cells correlated with perceived complexity; cells with elaborate process branching had larger fractal dimensions than cells with a simpler morphology. An analysis of changes in fractal dimension revealed distinct rates of growth for both oligodendrocytes and type 2 astrocytes. The fractal dimension remained constant over a 10-fold range in optical magnification, demonstrating that cultured O2A **glial** cells exhibit self-similarity, a defining characteristic of fractal objects. These results illustrate that fractal dimension analysis of maturing **cell** populations is a useful method for quantitatively describing the process of **cell** differentiation.

2001

16/3,AB/35 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13113884 BIOSIS NO.: 200100321033
Adult corneal epithelium as a potential source of **neural** progenitors.
AUTHOR: Ahmad I(a); Zhao X(a)
AUTHOR ADDRESS: (a)Ophthalmology, Nebraska Medical Center, Omaha, NE**USA
JOURNAL: IOVS 42 (4):pS197 March 15, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Association for Research in Vision and Ophthalmology Fort Lauderdale, Florida, USA April 29-May 04, 2001
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English
2001

16/3,AB/36 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13054329 BIOSIS NO.: 200100261478
Establishment of human **neural cell** lines derived from fetal

telencephalon.
AUTHOR: Paik Doo Jin(a); Yoo Young Mi(a); Cho Won Gil(a); Youn Jeehee(a); Chung Ho Sam(a); Chung Kyung Won
AUTHOR ADDRESS: (a)Hanyang University, 17 Haengdang-dong, Sungdong-gu, Seoul, 133-791**South Korea
JOURNAL: FASEB Journal 15 (5):pA1074 March 8, **2001**
MEDIUM: print
CONFERENCE/MEETING: Annual Meeting of the Federation of American Societies for Experimental Biology on Experimental Biology 2001 Orlando, Florida, USA March 31-April 04, 2001
ISSN: 0892-6638
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Cellular diversity in the mammalian central nervous system. (CNS) is originated from precursor cells present in the **neural** ectoderm. The multipotent stem cells rapidly proliferate to give rise to transiently dividing progenitors that eventually differentiate into several **cell** types of **neural** cells. These stem cells have been shown to be isolated from the embryonic CNS of several experimental animals and demonstrated to retain properties of immature cells such as nestin expression, extended proliferative potential and the capacity to differentiate to diverse lineages of **neural** cells. However, in vitro manipulation of human neuronal stem cells remains to be further studied, although this subject is interested in terms of clinical application. To establish human **neural cell** lines, we isolated **neural** stem cells from human fetal telencephalon. Upon in vitro primary **culture**, these cells readily formed nestin positive-clumps, indicating the proliferation of undifferentiated cells. The cells were resuspended and cultured on polycation treated plates to maintain adherent progenies. The adherent cells exhibited both phenotypes of neuronal and **glial** cells when characterized using an immunocytochemical analysis, suggesting **progenitor** cells differentiated into two diverse lineage of **neural** cells. These phenotypes were maintained in vitro until the **cell** lines were passaged at least six times. Thus, these results demonstrate that human **neural** stem **cell** lines derived from human fetal telencephalon were stably established and provide a therapeutic potential of cultured **neural** cells for **cell** regeneration and replacement in human degenerative diseases of nervous system.

2001

16/3,AB/37 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

13019501 BIOSIS NO.: 200100226650
Selective introduction of antisense oligonucleotides into single adult CNS **progenitor** cells using electroporation demonstrates the requirement of STAT3 activation for CNTF-induced gliogenesis.
AUTHOR: Aberg Maria A I(a); Ryttsen Frida; Hellgren Gunnel; Lindell Kajsa; Rosengren Lars E(a); MacLennan A John; Carlsson Bjorn; Orwar Owe; Eriksson Peter S(a)
AUTHOR ADDRESS: (a)Institute of Clinical Neuroscience, Sahlgrenska University Hospital, Goteborg University, SE-413 45, Goteborg**Sweden
JOURNAL: Molecular and Cellular Neuroscience 17 (3):p426-443 March, **2001**
MEDIUM: print
ISSN: 1044-7431
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We have developed a novel method in which antisense DNA is selectively electroporated into individual adult **neural progenitor** cells. By electroporation of antisense oligonucleotides against signal transducer and activator of transcription 3 (STAT3) we demonstrate that ciliary neurotrophic factor (CNTF) is an instructive signal for astroglial type 2 **cell** fate specifically mediated via activation of STAT3. Activation of the mitogen-activated protein kinase (MAPK) signaling pathway induced only a transient increase in **glial** fibrillary acidic protein (GFAP) expression, and inhibition of this signaling pathway did not block the induction by CNTF of **glial** differentiation in **progenitor** cells. In addition we show that microelectroporation is a new powerful method for introducing antisense agents into single cells in complex cellular networks.

2001

16/3,AB/38 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12901585 BIOSIS NO.: 200100108734
Generation and molecular characterisation of olfactory **progenitor** neurospheres.
AUTHOR: Cunningham A(a); Bieri S; Nichol K; Khan M
AUTHOR ADDRESS: (a)The Garvan Institute of Medical Research, Darlinghurst** Australia
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-60413
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The olfactory neuronal system is unique in maintaining a **progenitor** population which continues to proliferate and generate new neurones in the adult. Studies using retroviral infection of regenerating neuroepithelium have supported the existence of a multipotent olfactory **progenitor** in the basal region of the neuroepithelium which gives rise to both sustentacular, or supporting cells, and neurones (Huard et al, !998). This **progenitor** resides in the globose basal **cell**(GBC) population and it is likely that this stem **cell** might differ significantly from the relatively dormant pools of stem cells found in other areas of CNS, eg. the subventricular zone. We have isolated putative olfactory **progenitor** cells from neonatal rat olfactory tissue and in primary **culture** they form large multicellular aggregates, or neurospheres. The cells in the neurospheres expressed nestin, the intermediate filament protein widely used as marker of proliferating **neural** stem cells, and also labelled with GBC-1, a monoclonal antibody that recognises GBCs (Goldstein & Schwob, 1996). We were able to promote proliferation of neurospheres and differentiation down the neuronal pathway by treatment with specific exogenous growth factors. Single neurospheres were manually collected for RNA preparation and PCR performed using oligonucleotides specific for nestin, the olfactory neuronal transcription factor, Olf-1, GAP-43, beta-tubulin and GFAP. This molecular analysis confirmed expression of mRNAs for nestin and the neuronal markers and we were able

to examine dynamic alterations in these gene transcripts on exogenous application of specific trophic factors. This in viro model of neurogenesis will allow us to define the molecular characteristics of olfactory **progenitor** cells and further explore their pluripotentiality.

2000

16/3,AB/39 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12896915 BIOSIS NO.: 200100104064
Human embryonic germ **cell** derivatives express a broad range of developmentally distinct markers and proliferate extensively in vitro.
AUTHOR: Shamblott Michael J; Axelman Joyce; Littlefield John W; Blumenthal Paul D; Huggins George R; Cui Yan; Cheng Linzhao; Gearhart John D(a)
AUTHOR ADDRESS: (a)Department of Gynecology and Obstetrics, Johns Hopkins University School of Medicine, Baltimore, MD, 21287: gearhart@jhmi.edu** USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 98 (1):p113-118 January 2, **2001**
MEDIUM: print
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Human pluripotent stem cells (hPSCs) have been derived from the inner **cell** mass cells of blastocysts (embryonic stem cells) and primordial germ cells of the developing gonadal ridge (embryonic germ cells). Like their mouse counterparts, hPSCs can be maintained in **culture** in an undifferentiated state and, upon differentiation, generate a wide variety of **cell** types. Embryoid body (EB) formation is a requisite step in the process of in vitro differentiation of these stem cells and has been used to derive neurons and glia, vascular endothelium, hematopoietic cells, cardiomyocytes, and glucose-responsive insulin-producing cells from mouse PSCs. EBs generated from human embryonic germ **cell** cultures have also been found to contain a wide variety of **cell** types, including **neural** cells, vascular endothelium, muscle cells, and endodermal derivatives. Here, we report the isolation and **culture** of cells from human EBs as well as a characterization of their gene expression during growth in several different **culture** environments. These heterogeneous **cell** cultures are capable of robust and long-term (>70 population doublings (PD)) proliferation in **culture**, have normal karyotypes, and can be cryopreserved, clonally isolated, and stably transfected. **Cell** cultures and clonal lines retain a broad pattern of gene expression including simultaneous expression of markers normally associated with cells of **neural**, vascular/hematopoietic, muscle, and endoderm lineages. The growth and expression characteristics of these EB-derived cells suggest that they are relatively uncommitted precursor or **progenitor** cells. EB-derived cells may be suited to studies of human **cell** differentiation and may play a role in future transplantation therapies.

2001

16/3,AB/40 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12890597 BIOSIS NO.: 200100097746
Neurotropic virus as a molecular marker to distinguish **glial** and neuronal **progenitor** cells.
AUTHOR: Messam C A(a); Hou J; Major E O
AUTHOR ADDRESS: (a)NINDS/NIH, Bethesda, MD**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-4011
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Several neurotropic viruses selectively infect subtypes of human CNS cells. The polyoma virus JC, for example, primarily infects and degenerates oligodendrocytes in the human brain, resulting in the demyelinating disease, progressive multifocal leukoencephalopathy. Although the virus can bind to the surface of several **cell** types in vitro, JC virus infects human fetal brain (HFB) derived astrocytes but not neuronal cells. Susceptibility to infection appears to depend on the availability of cellular factors within target cells, suggesting the virus can distinguish between **glial** and neuronal cells at the molecular level. The goal of this study was to determine whether JC virus could distinguish between **glial** and neuronal **progenitor** cells. HFB derived multipotential CNS **progenitor** cells were isolated and propagated in **culture** using serum free defined medium containing epidermal growth factor and basic fibroblast growth factor. RT-PCR, Western blot and immunocytochemistry demonstrate that these **progenitor** cells express the stem **cell** marker nestin, but do not express differentiated **glial** or neuronal **cell** markers. The **progenitor** cells can be differentiated to produce astrocytes expressing GFAP and neurons expressing MAP-2. Following infection, JC virus genome was detected by in situ hybridization and late viral protein, VP-1, was detected by Western blot and immunocytochemistry. Intact virion particles were detected by hemagglutination assay. These studies can determine when JC virus susceptible **progenitor** cells differentiate into **glial** or neuronal cells and if viral susceptibility of **glial** or neuronal lineage cells is decided at the molecular level.
2000

16/3,AB/41 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12890073 BIOSIS NO.: 200100097222
Characteristics of rat **cell** lines produced with T155, a truncated SV40 large T polypeptide.
AUTHOR: Truckenmiller M E(a); Zhang P; Conejero C; Vawter M; Cheadle C; Becker K; Dillon-Carter O; Freed W J
AUTHOR ADDRESS: (a)Johns Hopkins Bayview Medical Center, Baltimore, MD**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-41516
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract

LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: For purposes of studying CNS developmental processes or for clinical applications such as **neural** transplantation, there is a great deal of interest in stem or **progenitor** cells that can differentiate into various **cell** types. Some CNS **cell** lines immortalized with oncogenes show some mutlipotential properties, primarily following CNS transplantation. We compared two clonal rat mesencephalic **cell** lines (AF5 and AC10) immortalized with T155, a truncated form of SV40 large T consisting of the N-terminal 155 amino acids. The AF5 **cell** line, but not AC10, shows multipotential properties under certain **culture** conditions: it is capable of spontaneous differentiation into both neuronal and **glial** phenotypes, facilitated by long-term maintenance in a closed vessel without a change in medium. The following analyses were performed on the two **cell** lines: karyotype, p53 gene mutation, p53 production, growth factor production (bFGF, PDGF, TGFbeta1, TGFbeta2), growth response to bFGF, telomere length and telomerase activity, and immunostaining for CNS antigens. Gene expression profiles by micro-array analysis were also performed comparing the AF5 **cell** line at log phase growth and in the differentiated/quiescent state. Although both **cell** lines had genetic abnormalities, no p53 gene mutations were observed and both **cell** lines exhibited p53 activation in response to adriomycin. Both **cell** lines produced significant amounts of PDGF and TGFbeta1, with AC10 producing the highest amounts. There were no differences in telomere length or telomerase activity in the AF5 cells over time (23 wks). Micro-array analyses of AF5 showed differences in gene expression associated with the differentiated vs. log-phase growth conditions.

2000

16/3,AB/42 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12885262 BIOSIS NO.: 200100092411
The amyloid precursor protein (APP) regulates human **neural progenitor cell** differentiation: implications for the disruption of its physiological role in Alzheimer's disease.
AUTHOR: Brannen C L(a); Qu T; Kumar V; Kaplan A; Sugaya K
AUTHOR ADDRESS: (a)The University of Illinois at Chicago, Chicago, IL**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-5036
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The capability for in vitro expansion of multipotent human **neural progenitor** cells (HNPs) may allow us to offer a well-characterized source of human stem-like cells for biomedical neuroscience research. We have previously reported (Brannen, C.L. et al., Neuroreport, 2000) that HNPs are differentiated into neurons (bIII-tubulin immuno-positive), astrocytes (**glial** fibrillary acidic protein immuno-positive), and oligodendrocytes (O4 immuno-positive) in a non-supplemented, serum-free basal medium (S-FrM). Furthermore, we have suggested that some endogenous factor/s may be involved in the

differentiation of HNPs in this **culture** condition. Using the TUNEL assay, we have successfully demonstrated that during the initial stages of HNP differentiation in the S-FrM condition, a population of these HNPs are dying by apoptosis. Thus, we have hypothesized that these apoptotic cells are releasing some differentiation factor/s. Because damaged neuronal cells are known to produce the amyloid precursor protein (APP), it is reasonable that APP may be a factor involved in the differentiation of HNPs. To investigate the effect of APP on the differentiation of HNPs under defined conditions, we have used the anti-APP monoclonal antibodies 22C11, 6E10, and 4G8 recognizing APP66-81, Abeta1-16, and Abeta17-23 respectively. Differentiation of HNPs was blocked by the addition of the 22C11 antibody; however, HNP differentiation was not inhibited by either 4G8 or 6E10. This finding implicates the involvement of the amino-terminal of APP in the regulation of HNP differentiation. To further examine the effect of APP on the differentiation of HNPs, we have added the secreted form of APP (sAPP) into the S-FrM HNP **culture**. In this condition, we are able to determine whether the differentiation of HNPs is influenced by the presence of sAPP in the extracellular milieu. This S-FrM HNP **culture** system provides an interesting model to further explore the involvement of APP in **neural** stem **cell** differentiation, a role that could have interesting implications for therapeutic strategies in Alzheimer's disease.

2000

16/3,AB/43 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12880928 BIOSIS NO.: 200100088077
Differentiation of human **neural** progenitors by Co-**culture** with oxidatively damaged human neuronal cells.
AUTHOR: Sugaya K(a); Brannen C L; Qu T
AUTHOR ADDRESS: (a)Univ. Illinois-Chicago, Chicago, IL**USA
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-31219
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We have previously reported that human **neural** progenitors (HNPs) can proliferate and differentiate into diverse CNS **cell** types (Brannen et al., 2000). The present study utilizes our HNP defined **culture** system in a co-**culture** experiment to identify possible interactions mediating the differentiation of these cells. Oxidative damage to human dopaminergic neuronal cells (SH-SY5H) induced differentiation of HNPs into neurons (betaIII-tubulin-positive), astrocytes (**glial** fibrillary acidic protein (GFAP)-positive), and oligodendrocytes (O4 -positive). HNPs seeded on **culture** plate membrane inserts were transferred to **culture** plates containing freshly prepared, serum-free defined medium and SH-SY5H exposed to varying concentrations of H2O2. Differentiation of HNPs was dose-dependent to the concentration of H2O2 used to cause oxidative damage to the SH-SY5H. Differentiation of HNPs following co-**culture** with SH-SY5H exposed to H2O2-induced oxidative damage results in a predominantly neuronal **cell** differentiation during the initial stages of co-**culture**; while **glial cell** types arise in experiments involving more extended co-**culture**. These results

suggest that factors producing oxidative damage on SH-SY5H may be sufficient to initiate neuronal differentiation of HNPs. Furthermore, it is possible that the differentiated HNPs produce factors, which may be acting via a regulatory feedback to further differentiate HNPs into astrocytes and oligodendrocytes. This co-**culture** system should continue to be useful for identifying differentiation factors involved in regulation of CNS repair elicited by **neural** stem cells in neurodegenerative disease.

2000

16/3,AB/44 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12879727 BIOSIS NO.: 200100086876
Self-renewable and neuronogliogenic **progenitor** (stem-like) cells comprise a major **cell** population of the radial **glial** system during neuronogenetic period in the mouse cerebral wall.
AUTHOR: Miyata T(a); Kawaguchi A; Okano H; Ogawa M
AUTHOR ADDRESS: (a)Brain Sci Inst, RIKEN, Wako**Japan
JOURNAL: Society for Neuroscience Abstracts 26 (1-2):pAbstract No-241
2000
MEDIUM: print
CONFERENCE/MEETING: 30th Annual Meeting of the Society of Neuroscience New Orleans, LA, USA November 04-09, 2000
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Radial **glial**' cells, characterized by their molphology in Golgi and RC2 staining, guide neuron migration. They are also proliferative but their cytogenetic capacity in vitro and their actual **cell** output in vivo are both unclear. We examined whether radial glia include self-renewable and multipotent stem-like cells using (1) the nestin-EGFP transgenic mice, (2) RC2 antibody, (3) BrdU labeling in utero, and (4) DiI labeling from the pial surface. Of the total ventricular zone (VZ) cells scraped from E14 cerebral slices, 60-70% were RC2+, while 70-80% were EGFP++ with a striking overlap with RC2. More than 90% of the VZ cells that were EGFP++DiI+ were also RC2+. Such EGFP++DiI+(RC2+) cells generated clones containing neurons and RC2+ cells (1-3d) and those composed of neurons and astrocytes (4-7d) in monolayer **culture**. They exhibited the persistent proliferative activity in floating aggregate ('neurosphere') **culture**. Although the EGFP++RC2+ cells were also highly proliferative in vivo during the neuronogenetic period (E13-15), their number remained constant, suggesting that the mode of their **cell** output is asymmetric. We observed that a single EGFP++DiI+(RC2+) E14 VZ **cell** generated one neuron and one RC2+ **cell** through its initial division in monolayer **culture**. Time-lapse observations in slice **culture** further evidenced the production of neurons from single DiI+ radial cells. Thus, the mid embryonic VZ stem/radial cells contribute to both neuronogenesis and construction of the cerebral cortical cytoarchitecture.

2000

16/3,AB/45 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12810398 BIOSIS NO.: 200100017547

Distinct roles for PI3K in proliferation and survival of oligodendrocyte **progenitor** cells.
AUTHOR: Ebner Sylvie; Dunbar Maryse; McKinnon Randall D(a)
AUTHOR ADDRESS: (a)UMDNJ-Robert Wood Johnson Medical School, 675 Hoes Lane, S-225, Piscataway, NJ, 08854: mckinnon@umdnj.edu**USA
JOURNAL: Journal of Neuroscience Research 62 (3):p336-345 November 1, **2000**
MEDIUM: print
ISSN: 0360-4012
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Phosphoinositol 3-kinase (PI3K) is a downstream effector for multiple ligand-activated receptors and modulates **cell** responses through activation of its target protein kinase B (Akt). We examined the roles of PI3K-Akt signaling in a primary **glial** (oligodendrocyte) **progenitor cell culture** system that is ligand-dependent for **cell** proliferation, survival, and prevention of differentiation. We demonstrate that PI3K and Akt (Ser-473 phosphorylation) are activated in response to platelet-derived growth factor but not basic fibroblast growth factor-2 (FGF2) and that distinct forms of PI3K are activated in early progenitors and later-maturation pro-oligodendroblasts as identified by their sensitivity to wortmannin. By establishing conditions to examine effects on **cell** proliferation and survival independently, we demonstrate that PI3K is necessary for a full mitogenic response and that PI3K is also necessary for early **progenitor** survival. Our results therefore demonstrate that PI3K-Akt signaling independently regulates proliferation and survival, that the form of PI3K is distinct in early progenitors and pro-oligodendroblasts, and that FGF2 does not activate this pathway in either primary **glial cell** population.

2000

16/3,AB/46 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12660010 BIOSIS NO.: 200000413512
Fibroblast growth factor-9 modulates the expression of myelin related proteins and multiple fibroblast growth factor receptors in developing oligodendrocytes.
AUTHOR: Cohen Rick I(a); Chandross Karen J
AUTHOR ADDRESS: (a)National Institutes of Health, National Institute of Neurological Disorders and Stroke, 9000 Rockville Pike, Building 36, Room 5D05, Bethesda, MD, 20892-4160**USA
JOURNAL: Journal of Neuroscience Research 61 (3):p273-287 August 1, **2000**
MEDIUM: print
ISSN: 0360-4012
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The effect of fibroblast growth factor (FGF)-9 on the expression of FGF receptors (FGFR) and the major myelin proteins was examined in cultures of developing rat brain oligodendrocytes (OLs), using immunological techniques. FGFR-1, -3, and -4 were expressed at all developmental stages but were not present in isolated myelin fractions. By contrast, FGFR-2 protein was predominantly localized to

differentiating cells and myelin. FGF-9 altered FGFR and myelin protein levels during OL differentiation; there was increased expression of FGFR-1 and decreased levels of both FGFR-2 and myelin proteins. Further, FGF-9 stimulated mitogen-associated protein kinase (MAPK) phosphorylation. The effect of FGF-9 on MAPK, however, was transient and less robust in **progenitor** cells than in differentiated oligodendrocytes. The effects of FGF-9 and FGF-2 on FGFR and myelin protein levels were comparable; both up-regulated FGFR-1, and down-regulated FGFR-2, CNP, PLP and MBP. These findings suggest that FGF-9 may be important for **glial cell** development.

2000

16/3,AB/47 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12619274 BIOSIS NO.: 200000372776
Three to four-year-old nonpassaged EGF-responsive **neural** **progenitor** cells: Proliferation, apoptosis, and DNA repair.
AUTHOR: Zhou F C(a); Kelley M R; Chiang Y H(a); Young P
AUTHOR ADDRESS: (a)Department of Anatomy/Cell Biology, and Medical Neurobiology Program, Indiana University School of Medicine, Indianapolis, IN, 46202**USA
JOURNAL: Experimental Neurology 164 (1):p200-208 July, **2000**
MEDIUM: print
ISSN: 0014-4886
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Epidermal growth factor responsive (EGFr) **neural** **progenitor** (NP) cells have been shown to be a potential alternative tissue source for **neural** transplantation and for developmental study. We have shown that nonpassaged EGFr NP cells can self-renew for 2 years in neurospheres and can robustly differentiate into glia and a number of neuronal **cell** types. We are now attempting to investigate if the EGFr NP cells will die or continue to live beyond the life span of the donor. In addition, we and other investigators have also found that EGFr NP cells, after transplant, retain only a small number of cells in the transplant site. In this study, we investigate the plasticity and fate of the EGFr NP cells. Using the nonpassaged method, we found EGFr NP cells live in the EGF supplement medium for over 4 years-the longest-lived EGFr NP cells ever reported. The 4-year-old striatal or cortical EGFr neurospheres, when subplated with substrate coating, migrate out of neurospheres and have robust growth with many processes. Furthermore, when nucleotide marker bromodeoxyuridine (BrdU) was added 3 days prior to the subplating, the EGFr NP cells were labeled positively with BrdU in the nucleus, indicating active proliferation activity. Meanwhile two other events were also found in the long-term EGFr NP cells. In the midst of the proliferation, apoptosis occurred. A subpopulation of EGFr NP cells are undergoing programmed **cell** death as indicated by the **cell** morphology and the TUNEL staining for DNA strand breaks. The TUNEL fluorescein-staining indicates that over 50% of EGFr NP cells are positive in the nuclei. On the other hand, we have also found that the major base excision repair enzyme, APE/ref-1, which is responsible for recognizing and repairing baseless sites in DNA, was present in the **progenitor** cells. However, in those cells undergoing apoptosis, APE/ref-1 levels were dramatically reduced or missing, and only a small percentage of cells were TUNEL and APE/ref-1 positive. These observations indicate that EGFr **neural** **progenitor** cells can live beyond the life span of the donor animal. The longevity of these

cells in **culture** may be enhanced due to decreased apoptosis and the retention of normal DNA repair capacity.

2000

16/3,AB/48 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12467853 BIOSIS NO.: 200000221355
Down-regulation of mu-opioid receptor expression in rat oligodendrocytes during their development in vitro.
AUTHOR: Tryoen-Toth P; Gaveriaux-Ruff C; Labourdette G(a)
AUTHOR ADDRESS: (a)Centre de Neurochimie, LNDR, UPR 1352 CNRS, 5 Rue Blaise Pascal, 67084, Strasbourg Cedex**France
JOURNAL: Journal of Neuroscience Research 60 (1):p10-20 April 1, **2000**
ISSN: 0360-4012
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In the central nervous system, opioid receptors are found in neurons and also in **glial** cells. To gain more information on their presence and possibly on their function, we investigated the expression of mu-opioid receptors (MOR) during oligodendroglial **cell** development in two **culture** systems. In these models, during the first days, the cells are O-2A bipotential **progenitor** cells (also called OPCs; oligodendrocyte precursor cells), and then they differentiate into oligodendrocytes, which mature. In the first system, oligodendroglial cells, derived from newborn rat brain hemispheres, are grown in primary **culture** in the presence of a confluent layer of astrocytes, and they differentiate slowly. In the second, cells are specifically detached from the mixed cultures of the first system and are grown thereafter alone in secondary **culture**, a condition allowing a rapid **cell** differentiation. Under both conditions OPCs and immature oligodendrocytes were found to express a high level of MOR mRNA, whereas mature oligodendrocytes did not express it at all. The decrease of MOR expression during oligodendrocyte maturation was progressive, suggesting that it was not a primary effect of differentiation but an indirect secondary effect. Our study also shows that basic fibroblast growth factor (bFGF), which has been claimed by some authors to induce a dedifferentiation of the mature oligodendrocytes, and retinoic acid (RA), which had not been tested before, were not able to restore MOR expression in mature oligodendrocytes. These results indicate that bFGF and RA neither reverse the maturation process nor dedifferentiate the cells. However, RA was found to inhibit almost completely the expression of the myelin basic protein. The main result of this study is that MOR is expressed in progenitors and in immature oligodendrocytes, but not in mature oligodendrocytes. This suggests that MOR could be involved in some developmental process of the cells of the oligodendroglial lineage.

2000

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S18          3   RD (unique items)
? s epidermal and basal and cell and glial
          114789  EPIDERMAL
          297295  BASAL
         3697248  CELL
           59464  GLIAL
     S19      42  EPIDERMAL AND BASAL AND CELL AND GLIAL
? s s19 not s18
              42  S19
               3  S18
     S20      39  S19 NOT S18
? rd
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              26  S21
         2544348  PY>1999
     S22       3  S21 AND PY>1999
? t s22/3,ab/all

 22/3,AB/1      (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13340838   BIOSIS NO.: 200100547987
Long-term proliferation and dopaminergic differentiation of human
  mesencephalic neural precursor cells.
AUTHOR: Storch A(a); Meissner W; Paul G; Boehm B O; Carvey P M; Kupsch A;
  Schwarz J
AUTHOR ADDRESS: (a)Dept. of Neurology, University of Ulm Med Sch, 89081,
  Ulm**Germany
JOURNAL: Society for Neuroscience Abstracts  27 (2):p1563 2001
MEDIUM: print
CONFERENCE/MEETING: 31st Annual Meeting of the Society for Neuroscience
San Diego, California, USA  November 10-15, 2001
ISSN: 0190-5295
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Dopamine neurons derived from neural CNS precursor cells expanded
  and differentiated in vitro might overcome the limited availability of
  appropriate tissue for restorative therapy in Parkinson's disease. Here,
  we report an improved method for long-term expansion and dopaminergic
  differentiation of human CNS precursor cells derived from the germinal
  region of fetal mesencephalon (6 to 9 weeks post fertilization) using
  serum-free media containing the mitogens EGF/FGF-2 and a reduction of
  atmospheric oxygen to 3%. Following incubation with striatal co-cultures
  from rat in differentiation media containing the cytokines IL-1b, IL-11,
  LIF and the growth factor GDNF, up to 1% of the precursor cells converted
  into cells immunoreactive for tyrosine hydroxylase (TH), a marker for
  dopamine neurons. These differentiated precursor cells exhibited four
  different DA neuron characteristics: TH and dopamine transporter, but no
  GABA expression, basal DA production and K+-evoked DA release.
  These precursor cells might serve as a useful source of human dopamine
  neurons for studying the development and degeneration of human dopamine
  neurons and may further serve as a continuous, on-demand source of cells
  for therapeutic transplantation in patients with Parkinson's disease.

2001


 22/3,AB/2      (Item 2 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
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13124994 BIOSIS NO.: 200100332143
Atlas of olfactory organs of Drosophila melanogaster 2. Internal organization and cellular architecture of olfactory sensilla.
AUTHOR: Shanbhag S R; Mueller B; Steinbrecht R A(a)
AUTHOR ADDRESS: (a)Max-Planck-Institut fuer Verhaltensphysiologie, 82319, Seewiesen: steinbrecht@mpi-seewiesen.mpg.de**Germany
JOURNAL: Arthropod Structure & Development 29 (3):p211-229 **2000**
MEDIUM: print
ISSN: 1467-8039
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Antennae and maxillary palps of Drosophila melanogaster were studied with the electron microscope on serial sections of cryofixed specimens. The number of **epidermal** cells roughly equals the number of sensilla, except for regions where the latter are scarce or absent. Each **epidermal cell** forms about two non-innervated spinules, a prominent subcuticular space and a conspicuous **basal** labyrinth, suggesting a high rate of fluid transport through the sensory epithelium. The internal organization and fine structure of trichoid, intermediate and basiconic sensilla is very similar. Receptor **cell** somata are invested by thin **glial** sheaths extending distad to the inner dendritic segments. Further distally, the thecogen **cell** forms a sleeve around the dendrites, but an extracellular dendrite sheath is absent. At the base of the cuticular apparatus, the inner sensillum-lymph space around the ciliary and outer dendritic segments is confluent with the large outer sensillum-lymph space formed by the trichogen and tormogen cells. All three auxiliary cells exhibit many features of secretory and transport cells but extend only thin **basal** processes towards the haemolymph sinus. The bauplan and fine structure of coeloconic sensilla differs in the following aspects: (1) the ciliary segment of the dendrites is located deeper below the base of the cuticular apparatus than in the other sensillum types; (2) a prominent dendrite sheath is always present, separating inner and outer sensillum-lymph spaces completely; (3) the apical microlamellae of the auxiliary cells are more elaborate, but free sensillum-lymph spaces are almost absent; (4) there are always four not three auxiliary cells. Morphometric data are presented on the diameter of inner and outer dendritic segments and on the size of receptor cells, as well as of the receptor and auxiliary **cell** nuclei. The special fine structural features of Drosophila olfactory sensilla are discussed under the aspects of sensillar function and the localization of proteins relevant for stimulus transduction.

2000

22/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12813928 BIOSIS NO.: 200100021077
Degradation of **glial** glutamate transporter mRNAs is selectively blocked by inhibition of cellular transcription.
AUTHOR: Zelenaia Olga A; Robinson Michael B(a)
AUTHOR ADDRESS: (a)3516 Civic Center Blvd., 502N Abramson Pediatric Research Bldg., Philadelphia, PA, 19104-4318: Robinson@pharm.med.upenn.edu**USA
JOURNAL: Journal of Neurochemistry 75 (6):p2252-2258 December, **2000**
MEDIUM: print

ISSN: 0022-3042
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Recent studies have demonstrated that the expression of the **glial** glutamate transporters GLT-1 (glutamate transporter 1) and GLAST (glutamate aspartate transporter) is regulated both in vivo and in vitro. For example, co-culturing with neurons, treatment with N6,2'-O-dibutyryladenosine 3':5'-cyclic monophosphate (dbcAMP), and treatment with **epidermal** growth factor all increase the steady-state levels of GLT-1 and GLAST protein in astrocyte cultures. These changes in protein expression are correlated with increased mRNA levels. In the present study, the degradation of GLT-1 and GLAST mRNAs was examined in control and dbcAMP-treated astrocyte cultures after inhibiting transcription with actinomycin D. Although one would predict that inhibition of transcription would cause a decrease in GLT-1 and GLAST mRNAs and that this decrease would depend on the rate of mRNA degradation, the levels of GLT-1 and GLAST mRNAs did not decrease even after 24 h of treatment with actinomycin D. Withdrawal of dbcAMP caused the levels of GLT-1 and GLAST mRNAs to fall to **basal** levels within 24 h, but this degradation was blocked if actinomycin D was added at the time of dbcAMP withdrawal. Importantly, actinomycin D did not block the degradation of c-fos mRNA also induced by dbcAMP in these cultures. Inhibition of translation with cycloheximide did not stabilize GLT-1 but partially attenuated the degradation of GLAST mRNA. Although the mechanism of this effect remains to be defined, these studies suggest that GLT-1 and GLAST mRNAs belong to a select class of inducible mRNAs stabilized by inhibitors of transcription. The possible relevance of these data to astrocyte differentiation is briefly discussed.

2000
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 s epidermal and basal and cell and neural and progenitor and glial
          114789  EPIDERMAL
          297295  BASAL
         3697248  CELL
          776852  NEURAL
           41327  PROGENITOR
           59464  GLIAL
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                  AND GLIAL
? rd
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     S18       3  RD (unique items)
? t s18/3,ab/all

 18/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File   5:Biosis Previews(R)
(c) 2002 BIOSIS. All rts. reserv.

10417910   BIOSIS NO.: 199699039055
Immunohistochemical analysis of in vivo patterns of bak expression, a
  proapoptotic member of the Bcl-2 protein family.
AUTHOR: Krajewski Stanislaw; Krajewska Maryla; Reed John C
AUTHOR ADDRESS:  Burnham Inst., 10901 North Torrey Pines Road, La Jolla, CA
  92037**USA
JOURNAL: Cancer Research  56 (12):p2849-2855 1996
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The in vivo patterns of bak gene expression were determined in
  human tissues using an immunohistochemical approach. Polyclonal antisera
  were raised in rabbits against a synthetic peptide corresponding to amino
  acids 14-36 of the human Bak protein, and were shown to be specific by
  immunoblot analysis of various human tissues and cell lines. Bak
  immunoreactivity was detected in a wide variety of cell types and
  was typically present within the cytosol in a punctuate pattern
  suggestive of association with intracellular organelles. Consistent with
  a proapoptotic role for the Bak protein, gradients of Bak protein
  production were observed in the complex epithelia of the nasopharynx,
  esophagus, colon, and bladder, with Bak immunointensity being highest in
  the upper layers and relatively low in the basal portions of these
  epithelia. Similarly, in the myeloid series of hematopoietic cells, Bak
  immunoreactivity was strongest in the terminally differentiated
  granulocytes, with only weak immunostaining occurring in most
  progenitor cells in the bone marrow. Among the other cell
  types and tissues with prominent Bak immunostaining were: (a)
  cardiomyocytes; (b) vascular and visceral smooth muscle cells; (c)
  basal cells of the prostate glands; (d) myoepithelial cells of the
  mammary glands; (e) distal convoluted tubules of the kidney; (f)
  epidermal keratinocytes; (g) enterocytes of the small intestine;
  (h) Sertoli and Leydig cells of the testes; (i) theca interna cells in
  the ovary; and (j) adrenal cortex (but not adrenal medulla). Nearly all
  neurons and glial cells of the central nervous system did not
  contain immunodetectable Bak protein, whereas sympathetic neurons as well
  as neurons in dorsal root ganglia and their axons were Bak
  immunopositive. Most circulating peripheral blood lymphocytes were
  negative for Bak immunostaining, whereas strong Bak immunoreactivity was
  found frequently in lymphocytes in the nodes and spleen. Overall, these
  patterns of bak expression are unique compared to other members of the
  bcl-2 gene family, and suggest that bak regulates cell death at
  specific stages of cell differentiation through tissue-specific
  control of its expression.
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1996

18/3,AB/2 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10340278 BIOSIS NO.: 199698795196
Morphological differentiation of astroglial **progenitor** cells from EGF-responsive neurospheres in response to fetal calf serum, basic fibroblast growth factor, and retinol.
AUTHOR: Chiang Yung H; Silani Vincenzo; Zhou Feng C(a)
AUTHOR ADDRESS: (a)Dep. Anatomy, MS 508, Indiana Univ. Sch. Med., 635 Barnhill Dr., Indianapolis, IN 46202**USA
JOURNAL: Cell Transplantation 5 (2):p179-189 1996
ISSN: 0963-6897
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Procurement of multipotential neuroglial stem cells is possible with the addition of **epidermal** growth factor (EGF). Stem cells will differentiate into neurons and glia upon the removal of EGF from the culture medium. We have previously characterized the neuronal differentiation of stem cells derived from long-term cultured nonpassage neurospheres. In the current study, we (1) characterize the morphological differentiation of the astroglial **progenitor cell** from 3-mo-old neurospheres, (2) examine whether the astroglial **progenitor** cells from neurospheres of different brain areas exhibit different differentiation responses to the same exogenous signals, and (3) test the effects of basic fibroblast growth factor (bFGF) and retinol on differentiation. Cerebral cortex, striatum, and mesencephalon cells were obtained from Embryonic Day 14 (E-14) rat fetuses and were dissociated for the procurement of neurospheres in chemically defined medium supplemented with EGF. After 3 mo in culture, the neurospheres, derived from each of the three brain areas, were subcultured into three groups on chamber slides: (1) **basal** medium, (2) the **basal** medium plus 20 ng/mL bFGF, and (3) the **basal** medium plus 10 mu-M retinol. Phenotypic expression of astroglial cells was examined after 14 days subculture. Our findings indicate that the 3-mo-old cultured nonpassage neurospheres contained numerous multipotential stem cells that stained positive with nestin, and that environmental factors played an important role in influencing the differentiation of astroglial **progenitor** cells. As detected by **glial** fibrillary acid protein (GFAP), astroglial **progenitor** cells turned into protoplasmic astrocytes in the FCS-containing **basal** medium, fibrous astrocytes in the presence of bFGF, and spindle-shaped astrocytes in the presence of retinol. There were no noticeable differences in differentiation among astroglial **progenitor** cells of the various brain region-derived neurospheres in any of the three medium conditions. Peculiar varicosity- and growth cone-like structures on the long slender GFAP-positive processes suggest that neuroblasts and glioblast may share common morphologies, features, or common **progenitor** cells during initial differentiation in vitro.

1996

18/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10325044 BIOSIS NO.: 199698779962
Plasticity of astrocytes derived from aged mouse cerebral hemispheres:

Changes with **cell** passage and immortalization.
AUTHOR: Grove Jerome; Gomez Julissa; Kentroti Susan; Vernadakis Antonia(a)
AUTHOR ADDRESS: (a)Dep. Pharmacol., Univ. Colo. Health Sci. Cent., 4200 E. 9th Ave., Denver, CO 80206**USA
JOURNAL: Brain Research Bulletin 39 (4):p211-217 1996
ISSN: 0361-9230
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: This study was targeted at the beginning to understand the functional status of **glial** cells derived from aged brain. We have previously characterized passaged **cell** cultures derived from aged mouse cerebral hemispheres (MACH) and found them to contain large populations of astrocytes, type 1, as well as limited numbers of astrocytes, type 2, oligodendrocytes, and **progenitor** cells. Using the activity of the astrocyte marker, glutamine synthetase (GS), as an index, we found that MACH astrocytes continue to respond to several microenvironmental signals, including the cAMP-enhancing agents dibutyryl cAMP and R020-1724 (an inhibitor of phosphodiesterase). In addition, whereas the **basal** activity of GS increased with **cell** passage, their response to these agents was **cell**-passage dependent, increasing at early (21-22) passages and decreasing at later (4651) passages. Because neurotrophins (i.e., NGF and EGF) also provide microenvironmental signals essential to normal **glial** function, MACH cultures were assessed for their response to these factors. MACH cultures at passage 35 responded to treatment with NGF and EGF with a dose-dependent increase in GS activity by both neurotrophins. With the intention of arresting these cultures at a specific stage of differentiation, these cells were immortalized at passage 19 by transfection with the gene encoding SV40 Large T antigen. These immortalized MACH responded to exposure to dBcAMP and R020-1724 with a marked decrease in GS activity, mimicking the response of normal MACH glia at late passage. Finally, because it has been shown that glia from both immature and adult brain contain neurotrophins and respond to neurotrophins via a receptor-mediated pathway, we examined expression of NGF protein as well as NGF (p-75) and EGF receptor protein in various passages and colonies of normal and immortalized MACH cultures. We found a consistent expression of all three proteins in the various **cell** populations. Results of this study suggest that astrocytes from aging brain continue to function normally with respect to several parameters (i.e., response to neurotrophins and differentiating agents). Thus, they retain their plasticity to a great degree through early **cell** passages. However, with advancing **cell** passage this plasticity declines and **cell** homeostasis is impaired. We propose, therefore, that astrocytes undergo several critical periods in their functional lifespan, one of which is represented by the functional transition demonstrated in this study.

1996
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Set     Items   Description
S1        844   GLIAL AND REVIEW AND PY<1999
S2          0   S1 AND BASAL AND CULTURE
S3         39   S1 AND CULTURE
S4         32   RD (unique items)
S5        252   GLIAL AND REVIEW AND PY>1999
S6         18   S5 AND CULTURE
S7         13   RD (unique items)
S8       4426   (NERVE OR NEURAL) AND CELL AND CULTURE AND PY>1999
S9         46   S8 AND REVIEW
S10        39   RD (unique items)
S11        34   S10 NOT S1-S7
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           59464  GLIAL
     S13     633  S12 AND GLIAL
? s s13 and progenitor
             633  S13
           41327  PROGENITOR
     S14      63  S13 AND PROGENITOR
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         2544348  PY>1999
     S16      48  S15 AND PY>1999
? t s16/3,ab/all

 16/3,AB/1     (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

13289106   22071220   PMID: 12075991
  Human umbilical cord blood cells can be induced to express markers for
neurons and glia.
  Bicknese Alma R; Goodwin Holly S; Quinn Cheryl O; Henderson Verneake C D;
Chien Shin-Nan; Wall Donna A
  Department of Neurology, Saint Louis University, and Cardinal Glennon
Children's Hospital, MO 63110, USA. bicknese@slu.edu
  Cell transplantation (United States)  2002,  11  (3)  p261-4,
ISSN 0963-6897   Journal Code: 9208854
  Document type: Journal Article
  Languages: ENGLISH
  Main Citation Owner: NLM
  Record type: In Process
  Rare cells are present in human umbilical cord blood that do not express
the hematopoietic marker CD45 and in culture do not produce cells of
hematopoietic lineage. These umbilical cord multipotent stem cells (UC-MC)
behave as multilineage progenitor cells (stem cells) and can be
expanded in tissue culture . Exposure to basic fibroblast growth
factor (bFGF) and human epidermal growth factor (hEGF) for a minimum of 7
days in culture induces expression of neural and glial
markers. Western immunoblots demonstrate expression of both beta-tubulin
III and glial fibrillary acidic protein (GFAP). Immunocytochemistry
of the cells showed intense labeling to both compounds on the intracellular
cytoskeleton.     The    oligodendrocyte    cell    surface    marker
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galactocerebroside (Gal-C) was present on most cells. Many cells show dual labeling, expressing both neuronal and **glial** markers.

16/3,AB/2 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12880427 21665906 PMID: 11807037
Pax6 is required to regulate the **cell** cycle and the rate of progression from symmetrical to asymmetrical division in mammalian cortical progenitors.
Estivill-Torrus Guillermo; Pearson Helen; van Heyningen Veronica; Price David J; Rashbass Penny
Department of Biomedical Sciences, University of Edinburgh Medical School, Hugh Robson Building, George Square, Edinburgh EH8 9XD, UK.
Development (Cambridge, England) (England) Jan **2002**, 129 (2) p455-66, ISSN 0950-1991 Journal Code: 8701744
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
In the proliferative zone of the developing cerebral cortex, multipotential progenitors predominate early in development and divide to increase the **progenitor** pool. As corticogenesis progresses, proportionately fewer progenitors are produced and, instead, **cell** divisions yield higher numbers of postmitotic neurones or **glial** cells. As the switch from the generation of progenitors to that of differentiated cells occurs, the orientation of **cell** division alters from predominantly symmetrical to predominantly asymmetrical. It has been hypothesised that symmetrical divisions expand the **progenitor** pool, whereas asymmetrical divisions generate postmitotic cells, although this remains to be proved. The molecular mechanisms regulating these processes are poorly understood. The transcription factor Pax6 is highly expressed in the cortical proliferative zone and there are morphological defects in the Pax6(Sey/Sey) (Pax6 null) cortex, but little is known about the principal cellular functions of Pax6 in this region. We have analysed the **cell** -cycle kinetics, the **progenitor** cleavage orientation and the onset of expression of differentiation markers in Pax6(Sey/Sey) cortical cells in vivo and in vitro. We showed that, early in corticogenesis at embryonic day (E) 12.5, the absence of Pax6 accelerated cortical development in vivo, shortening the **cell** cycle and the time taken for the onset of expression of **neural** -specific markers. This also occurred in dissociated **culture** of isolated cortical cells, indicating that the changes were intrinsic to the cortical cells. From E12.5 to E15.5, proportions of asymmetrical divisions increased more rapidly in mutant than in wild-type embryos. By E15.5, interkinetic nuclear migration during the **cell** cycle was disrupted and the length of the **cell** cycle was significantly longer than normal in the Pax6(Sey/Sey) cortex, with a lengthening of S phase. Together, these results show that Pax6 is required in developing cortical progenitors to control the **cell** -cycle duration, the rate of progression from symmetrical to asymmetrical division and the onset of expression of **neural**-specific markers.

16/3,AB/3 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12803683 21634363 PMID: 11771935
Transplantation of human **neural progenitor** cells into the neonatal rat brain: extensive migration and differentiation with long-distance axonal projections.
Englund Ulrica; Fricker-Gates Rosemary A; Lundberg Cecilia; Bjorklund Anders; Wictorin Klas
Wallenberg Neuroscience Center, Division of Neurobiology, Lund

University, S-221 84 Lund, Sweden.
Experimental neurology (United States) Jan **2002**, 173 (1) p1-21
, ISSN 0014-4886 Journal Code: 0370712
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Here we examined the ability of human **neural** progenitors from the embryonic forebrain, expanded for up to a year in **culture** in the presence of growth factors, to respond to environmental signals provided by the developing rat brain. After survival times of up to more than a year after transplantation into the striatum, the hippocampus, and the subventricular zone, the cells were analyzed using human-specific antisera and the reporter gene green fluorescent protein (GFP). From grafts implanted in the striatum, the cells migrated extensively, especially within white matter structures. Neuronal differentiation was most pronounced at the striatal graft core, with axonal projections extending caudally along the internal capsule into mesencephalon. In the hippocampus, cells migrated throughout the entire hippocampal formation and into adjacent white matter tracts, with differentiation into neurons both in the dentate gyrus and in the CA1-3 regions. Directed migration along the rostral migratory stream to the olfactory bulb and differentiation into granule cells were observed after implantation into the subventricular zone. **Glial** differentiation occurred at all three graft sites, predominantly at the injection sites, but also among the migrating cells. A lentiviral vector was used to transduce the cells with the GFP gene prior to grafting. The reporter gene was expressed for at least 15 weeks and the distribution of the gene product throughout the entire cytoplasmic compartment of the expressing cells allowed for a detailed morphological analysis of a portion of the grafted cells. The extensive integration and differentiation of in vitro-expanded human **neural progenitor** cells indicate that multipotent progenitors are capable of responding in a regionally specific manner to cues present in the developing rat brain. (c)2002 Elsevier Science.

16/3,AB/4 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12792932 21375894 PMID: 11482885
Neuronal differentiation of mouse embryonic stem cells: lineage selection and forced differentiation paradigms.
O'Shea K S
Department of Cell and Developmental Biology, 4748 MSII Building, University of Michigan Medical School, Ann Arbor, MI 48109-0616, USA. oshea@umich.edu
Blood cells, molecules & diseases (United States) May-Jun **2001**, 27 (3) p705-12, ISSN 1079-9796 Journal Code: 9509932
Contract/Grant No.: NS-39438; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Primitive embryonic stem cells are an ideal starting **cell** population for studies of gene expression and lineage segregation during development. Despite their potential, it has been difficult to determine **culture** conditions that cause single-lineage differentiation of these pluripotent cells. Both genetic and epigenetic approaches have been taken to promote neuronal differentiation of embryonic stem cells, including aggregation, exposure to the nonspecific teratogen/morphogen retinoic acid, low-density **culture**, exposure to growth/differentiation factors, and forced differentiation following expression of lineage-restricted "developmental control" genes. In the current investigation, a hybrid approach involving genetic techniques of "lineage selection" or "forced

differentiation" has been employed to develop primitive **neural progenitor cell** lines. These lines form an important starting point to examine the cascades of gene expression (and inhibition) during neuronal and **glial** lineage segregation, to study growth factor effects on **neural** differentiation, and ultimately to provide a source of cells for transplantation to a damaged nervous system. Copyright 2001 Academic Press.

16/3,AB/5 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12777534 21668336 PMID: 11810020
Neural progenitors isolated from newborn rat spinal cords differentiate into neurons and astroglia.
Tzeng S F
Department of Biology, National Cheng-Kung University, Tainan, Taiwan, ROC.
Journal of biomedical science (Switzerland) Jan-Feb **2002**, 9 (1) p10-6, ISSN 1021-7770 Journal Code: 9421567
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: In Process
Permanent functional deficit in patients with spinal cord injury (SCI) is in part due to severe **neural cell** death. Therefore, **cell** replacement using stem cells and **neural** progenitors that give rise to neurons and glia is thought to be a potent strategy to promote tissue repair after SCI. Many studies have shown that stem cells and **neural** progenitors can be isolated from embryonic, postnatal and adult spinal cords. Recently, we isolated **neural** progenitors from newborn rat spinal cords. In general, the **neural** progenitors grew as spheres in **culture**, and showed immunoreactivity to a **neural progenitor** cellular marker, nestin. They were found to proliferate and differentiate into **glial** fibrillary acidic protein-positive astroglia and multiple neuronal populations, including GABAergic and cholinergic neurons. Neurotrophin 3 and neurotrophin 4 enhanced the differentiation of **neural** progenitors into neurons. Furthermore, the **neural** progenitors that were transplanted into contusive spinal cords were found to survive and have migrated in the spinal cord rostrally and caudally over 8 mm to the lesion center 7 days after injury. Thus, the **neural** progenitors isolated from newborn rat spinal cords in combination with neurotrophic factors may provide a tool for **cell** therapy in SCI patients. Copyright 2002 National Science Council, ROC and S. Karger AG, Basel

16/3,AB/6 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12610325 21555346 PMID: 11698597
Multipotent stem cells from the mouse basal forebrain contribute GABAergic neurons and oligodendrocytes to the cerebral cortex during embryogenesis.
He W; Ingraham C; Rising L; Goderie S; Temple S
Center for Neuropharmacology and Neuroscience, Albany Medical College, Albany, New York 12208, USA.
Journal of neuroscience : the official journal of the Society for Neuroscience (United States) Nov 15 **2001**, 21 (22) p8854-62, ISSN 1529-2401 Journal Code: 8102140
Contract/Grant No.: R01 NS33529; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed
During CNS development, **cell** migrations play an important role, adding to the cellular complexity of different regions. Earlier studies have shown a robust migration of cells from basal forebrain into the overlying dorsal forebrain during the embryonic period. These immigrant cells include GABAergic neurons that populate the cerebral cortex and hippocampus. In this study we have examined the fate of other basal forebrain cells that migrate into the dorsal forebrain, identifying basal cells using an antibody that recognizes both early (dlx1/2) and late (dlx 5/6) members of the dlx homeobox gene family. We found that a subpopulation of cortical and hippocampal oligodendrocytes are also ventral-derived. We traced the origin of these cells to basal multipotent stem cells capable of generating both GABAergic neurons and oligodendrocytes. A clonal analysis showed that basal forebrain stem cells produce significantly more GABAergic neurons than dorsal forebrain stem cells from the same embryonic age. Moreover, stem **cell** clones from basal forebrain are significantly more likely to contain both GABAergic neurons and oligodendrocytes than those from dorsal. This indicates that forebrain stem cells are regionally specified. Whereas dlx expression was not detected within basal stem cells growing in **culture**, these cells produced dlx-positive products that are capable of migration. These data indicate that the developing cerebral cortex incorporates both neuronal and **glial** products of basal forebrain and suggest that these immigrant cells arise from a common **progenitor**, a dlx-negative basal forebrain stem **cell**.

16/3,AB/7 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12547877 21434232 PMID: 11550218
Increase of oligodendrocyte **progenitor** cells after spinal cord injury.
Ishii K; Toda M; Nakai Y; Asou H; Watanabe M; Nakamura M; Yato Y; Fujimura Y; Kawakami Y; Toyama Y; Uyemura K
Department of Orthopaedic Surgery, Keio University School of Medicine, Shinjuku-ku, Tokyo, Japan.
Journal of neuroscience research (United States) Sep 15 **2001**, 65 (6) p500-7, ISSN 0360-4012 Journal Code: 7600111
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The reaction of oligodendrocyte **progenitor** cells (OPCs) after spinal cord injury (SCI) is poorly understood. In this study, we examined oligodendroglial reactions after contusion SCI in adult rats by immunohistochemistry. OPCs were identified by staining with monoclonal antibodies (mAbs) A2B5 and O4. Each of the A2B5-, O4-positive OPCs and galactocerebroside-positive oligodendrocytes dramatically increased in the lesion of the dorsal posterior funiculus. Bromodeoxyuridine (BrdU) incorporation studies showed that most O4-positive cells in the lesion were labeled with BrdU, suggesting that these OPCs were proliferative. In contrast, the expression of myelin basic protein was decreased in the lesion compared with controls that received laminectomy only. From the injured cord, OPCs were isolated by immunopanning with mAb A2B5. We observed an increased number of OPCs from the injured spinal cords compared with those isolated from controls and unoperated animals. After several days in **culture** , the OPCs from the lesion expressed galactocerebroside. These results suggest that OPCs are induced and can differentiate following SCI in the adult rat. Copyright 2001 Wiley-Liss, Inc.

16/3,AB/8 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

12513423 21321304 PMID: 11428508
An efficient method for the culturing and generation of neurons and astrocytes from second trimester human central nervous system tissue.
Barami K; Grever W E; Diaz F G; Lyman W D
Department of Neurosurgery, Wayne State University, Detroit, MI 48201, USA. kbarami@neurosurgery.wayne.edu
Neurological research (England) Jun **2001**, 23 (4) p321-6, ISSN 0161-6412 Journal Code: 7905298
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
The isolation, culturing and expansion of human **neural** progenitors cells has important potential clinical applications in cellular transplantation strategies as well as in developmental studies involving the central nervous system (CNS). This study describes an efficient method to **culture** neurons and astrocytes as primary cultures, as well as from proliferative **progenitor** cells derived from second trimester fetal CNS tissue. Second trimester fetal human tissue was mechanically dissociated and subjected to trypsin-dissociation and trituration. The resulting suspension was passed over a Percoll density gradient. The middle (second) fraction of cells was centrifuged to yield a homogenous population of cells with 80%-90% viability. These cells were either cultured directly on laminin coated dishes with defined medium supplemented with fetal bovine serum or in defined medium supplemented with growth factors including epidermal growth factor, basic fibroblast growth factor and leukemia inhibitory factor. The primary **cell** cultures yielded neurons and astrocytes after 3-5 days in vitro verified by immunostaining with MAP2ab and GFAP. Cells exposed to growth factor supplemented medium formed free-floating spheres within one week. Upon growth factor removal and plating on laminin-coated dishes, brain derived spheres gave rise to neurons, astrocytes and oligodendrocytes; spinal cord derived spheres generated only astrocytes. This protocol describes an efficient method to generate and **culture** neurons and astrocytes from second trimester human CNS tissue that may be useful in transplantation and developmental studies.

16/3,AB/9 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11366075 21453756 PMID: 11567613
Asymmetric inheritance of radial **glial** fibers by cortical neurons.
Miyata T; Kawaguchi A; Okano H; Ogawa M
Laboratory for Cell Culture Development, Brain Science Institute, RIKEN, 351-0198, Saitama, Japan. tmiyata@brain.riken.go.jp
Neuron (United States) Sep 13 **2001**, 31 (5) p727-41, ISSN 0896-6273 Journal Code: 8809320
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Recent studies demonstrated the neuronogenic role of radial **glial** cells (RGCs) in the rodent. To reveal the fate of radial **glial** processes, we intensively monitored divisions of RGCs in DiI-labeled slices from the embryonic day 14 mouse cortex. During RGC division, each pia-connected fiber becomes thin but is neither lost nor divided; it is inherited asymmetrically by one daughter **cell**. In divisions that produce a neuron and a **progenitor** , the neuron inherits the pial fiber, also grows a thick ventricular process for several hours, and is therefore indistinguishable from the **progenitor** RGC. The ventricular process in the radial **glial** -like neuron ("radial neuron") then collapses, leading to ascent of the neuron by using the "recycled" radial

fiber.

16/3,AB/10 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11346988 21411726 PMID: 11520124
A clonal line of mesencephalic **progenitor** cells converted to dopamine neurons by hematopoietic cytokines: a source of cells for transplantation in Parkinson's disease.
Carvey P M; Ling Z D; Sortwell C E; Pitzer M R; McGuire S O; Storch A; Collier T J
Department of Pharmacology, Rush-Presbyterian-St. Luke's Medical Center, Chicago, Illinois, USA.
Experimental neurology (United States) Sep **2001**, 171 (1) p98-108, ISSN 0014-4886 Journal Code: 0370712
Contract/Grant No.: AG17092; AG; NIA; AG600844; AG; NIA
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Neural progenitor cells potentially provide a limitless, on-demand source of cells for grafting into patients with Parkinson's disease (PD) if the signals needed to control their conversion into dopamine (DA) neurons could be identified. We have recently shown that cytokines which instruct **cell** division and differentiation within the hematopoeitic system may provide similar functions in the central nervous system. We have shown that mitotic **progenitor** cells can be isolated from embryonic rat mesencephalon and that these cells respond to a combination of interleukin-1, interleukin-11, leukemia inhibitory factor, and **glial cell** line-derived neurotrophic factor yielding a tyrosine hydroxylase-immunoreactive (THir) phenotype in 20-25% of total cells. In the present study, 24 clonal **cell** lines derived from single cells of mesencephalic proliferation spheres were examined for their response to the cytokine mixture. The clone yielding the highest percentage of THir neurons (98%) was selected for further study. This clone expressed several phenotypic characteristics of DA neurons and expression of Nurr1. The response to cytokines was stable for several passages and after cryopreservation for several months. When grafted into the striatum of DA-depleted rats, these cells attenuated rotational asymmetry to the same extent as freshly harvested embryonic DA neurons. These data demonstrate that mesencephalic **progenitor** cells can be clonally expanded in **culture** and differentiated in the presence of hematopoietic cytokines to yield enriched populations of DA neurons. When transplanted, these cells provide significant functional benefit in the rat model of PD. Copyright 2001 Academic Press.

16/3,AB/11 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11326992 21378377 PMID: 11485986
PDGF autocrine stimulation dedifferentiates cultured astrocytes and induces oligodendrogliomas and oligoastrocytomas from **neural** progenitors and astrocytes in vivo.
Dai C; Celestino J C; Okada Y; Louis D N; Fuller G N; Holland E C
Department of Neurosurgery, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
Genes & development (United States) Aug 1 **2001**, 15 (15) p1913-25, ISSN 0890-9369 Journal Code: 8711660
Contract/Grant No.: UO1CA894314-1; CA; NCI
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM

Record type: Completed
We present evidence that some low-grade oligodendrogliomas may be comprised of proliferating **glial progenitor** cells that are blocked in their ability to differentiate, whereas malignant gliomas have additionally acquired other mutations such as disruption of **cell** cycle arrest pathways by loss of Ink4a-Arf. We have modeled these effects in **cell culture** and in mice by generating autocrine stimulation of glia through the platelet-derived growth factor receptor (PDGFR). In **cell culture**, PDGF signaling induces proliferation of **glial** precursors and blocks their differentiation into oligodendrocytes and astrocytes. In addition, coexpression of PDGF and PDGF receptors has been demonstrated in human gliomas, implying that autocrine stimulation may be involved in glioma formation. In this study, using somatic **cell** type-specific gene transfer we investigated the functions of PDGF autocrine signaling in gliomagenesis by transferring the overexpression of PDGF-B into either nestin-expressing **neural** progenitors or **glial** fibrillary acidic protein (GFAP)-expressing astrocytes both in **cell culture** and in vivo. In cultured astrocytes, overexpression of PDGF-B caused significant increase in proliferation rate of both astrocytes and **neural** progenitors. Furthermore, PDGF gene transfer converted cultured astrocytes into cells with morphologic and gene expression characteristics of **glial** precursors. In vivo, gene transfer of PDGF to **neural** progenitors induced the formation of oligodendrogliomas in about 60% of mice by 12 wk of age; PDGF transfer to astrocytes induced the formation of either oligodendrogliomas or mixed oligoastrocytomas in about 40% of mice in the same time period. Loss of Ink4a-Arf, a mutation frequently found in high-grade human gliomas, resulted in shortened latency and enhanced malignancy of gliomas. The highest percentage of PDGF-induced malignant gliomas arose from of Ink4a-Arf null **progenitor** cells. These data suggest that chronic autocrine PDGF signaling can promote a proliferating population of **glial** precursors and is potentially sufficient to induce gliomagenesis. Loss of Ink4a-Arf is not required for PDGF-induced glioma formation but promotes tumor progression toward a more malignant phenotype.

16/3,AB/12 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11232245 21262942 PMID: 11370804
Neural precursor cells form rudimentary tissue-like structures in a rotating-wall vessel bioreactor.
Low H P; Savarese T M; Schwartz W J
Department of Neurology, University of Massachusetts Medical School, Worcester 01655, USA.
In vitro cellular & developmental biology. Animal (United States) Mar **2001**, 37 (3) p141-7, ISSN 1071-2690 Journal Code: 9418515
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
We have analyzed the biology of embryonic, epidermal growth factor-responsive murine **neural** precursor cells cultured in the high-aspect ratio vessel (HARV). Within 2-3 d of rotary-**cell culture** , such cells formed multiple, macroscopic, three-dimensional structures that were orders of magnitude larger than the cellular clusters ("neurospheres") formed by these cells in conventional stationary-flask cultures. Each HARV structure was composed of a multilayered cellular shell surrounding one or more central cavities that were bordered by pyknotic **cell** nuclei. Although the cells in the HARV structures were more pleomorphic than those in neurospheres, the structures did not appear to represent primitive **neural** tumors: the formation of HARV structures by precursor cells was not an irreversible phenotypic change, and the

structures did not originate from the clonal expansion of single-**progenitor** cells; the growth rate and invasiveness of the cells in HARVs were less than those in flasks; and HARV-cultured cells did not form tumors after subcutaneous inoculation into the flanks of NOD-scid/scid mice. Immunohistochemical analysis suggested that HARV structures might be novel "prototissues" characterized by a crude, but organized, architecture, with a surface layer of immature proliferating cells (nestin- and proliferating **cell** nuclear antigen-positive) that enclosed strata of more differentiated cells (beta-tubulin III- and **glial** fibrillary acidic protein-positive) within. Rotary-**cell culture** may have significant implications for the eventual utility of **neural** precursors for clinical neurotransplantation.

16/3,AB/13 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11219324 21226496 PMID: 11329183
AN2/NG2 protein-expressing **glial progenitor** cells in the murine CNS: isolation, differentiation, and association with radial glia.
Diers-Fenger M; Kirchhoff F; Kettenmann H; Levine J M; Trotter J
Department of Neurobiology, University of Heidelberg, Heidelberg, Germany.
Glia (United States) May **2001**, 34 (3) p213-28, ISSN 0894-1491 Journal Code: 8806785
Contract/Grant No.: NS 21198; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
During early **neural** development, the lineage specification of initially pluripotent **progenitor** cells is associated with proliferation, differentiation, and migration. Oligodendroglial **progenitor** cells migrate from their sites of origin to reach the axons that they will myelinate. We have described a **cell**-surface protein, AN2, expressed by oligodendroglial **progenitor** cells in vitro and showed that antibodies against AN2 inhibited the migration of cultured primary oligodendroglial **progenitor** cells, suggesting that the AN2 antigen plays a role in their migration. Recently, results from MALDI mass spectroscopy showed that AN2 is the mouse homologue of the rat NG2 protein. In this study, we have analyzed cells staining with AN2 antibodies during development and in the adult murine central nervous system (CNS), carried out double stainings with antibodies against NG2, and investigated the differentiation potential of cells in vitro after isolation from early postnatal brain using AN2 antibodies. AN2 and NG2 antibodies stained totally overlapping populations of cells in the CNS. AN2/NG2 expressing cells in embryonic and postnatal brain expressed the PDGF-alpha-receptor and in postnatal brain exhibited electrophysiological properties typical of **glial progenitor** cells. Cells isolated from early postnatal brain using AN2 monoclonal antibody developed into oligodendrocytes in low serum medium or into astrocytes in the presence of fetal calf serum. In the embryonic spinal cord, cells staining with AN2 antibodies were found closely apposed to radial **glial** cells, suggesting that **glial** precursors, like neurons, may use radial glia as scaffolds for migration.

16/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

11120498 21125880 PMID: 11071894
Pescadillo, a novel **cell** cycle regulatory protein abnormally expressed in malignant cells.
Kinoshita Y; Jarell A D; Flaman J M; Foltz G; Schuster J; Sopher B L;

Irvin D K; Kanning K; Kornblum H I; Nelson P S; Hieter P; Morrison R S
Department of Neurological Surgery, University of Washington School of Medicine, Seattle, Washington 98195, USA.
Journal of biological chemistry (United States) Mar 2 **2001**, 276 (9) p6656-65, ISSN 0021-9258 Journal Code: 2985121R
Contract/Grant No.: CA75173; CA; NCI; NS35533; NS; NINDS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Using a **culture** model of **glial** tumorigenesis, we identified a novel gene that was up-regulated in malignant mouse astrocytes following the loss of p53. The gene represents the murine homologue of pescadillo, an uncharacterized gene that is essential for embryonic development in zebrafish. Pescadillo is a strongly conserved gene containing unique structural motifs such as a BRCA1 C-terminal domain, clusters of acidic amino acids and consensus motifs for post-translational modification by SUMO-1. Pescadillo displayed a distinct spatial and temporal pattern of gene expression during brain development, being detected in **neural progenitor** cells and postmitotic neurons. Although it is not expressed in differentiated astrocytes in vivo, the pescadillo protein is dramatically elevated in malignant human astrocytomas. Yeast strains harboring temperature-sensitive mutations in the pescadillo gene were arrested in either G(1) or G(2) when grown in nonpermissive conditions, demonstrating that pescadillo is an essential gene in yeast and is required for **cell** cycle progression. Consistent with the latter finding, DNA synthesis was only observed in mammalian cells expressing the pescadillo protein. These results suggest that pescadillo plays a crucial role in **cell** proliferation and may be necessary for oncogenic transformation and tumor progression.

16/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10816842 20359594 PMID: 10899225
Immunocytochemical and physiological characterization of a population of cultured human **neural** precursors.
Piper D R; Mujtaba T; Rao M S; Lucero M T
Department of Physiology, University of Utah School of Medicine, Salt Lake City 84108, Utah, USA.
Journal of neurophysiology (UNITED STATES) Jul **2000**, 84 (1) p534-48, ISSN 0022-3077 Journal Code: 0375404
Contract/Grant No.: DC-82994; DC; NIDCD; NO1-HD-7-3263; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Human **neural** precursor cells (HNPC) have recently become commercially available. In an effort to determine the usefulness of these cells for in vitro studies, we have grown cultured HNPCs (cHNPCs) according to the supplier specifications. Here we report our characterization of cHNPCs under nondifferentiating and differentiating growth conditions and make a comparison to primary HNPCs (pHNPCs) obtained at the same developmental time point from a different commercial supplier. We found that under nondifferentiating conditions, cHNPCs expressed nestin, divided rapidly, expressed few markers of differentiated cells, and displayed both 4-aminopyridine (4-AP)-sensitive and delayed-rectifier type K(+) currents. No inward currents were observed. On changing to differentiating **culture** conditions, a majority of the cells expressed neuronal markers, did not divide, expressed inward and outward time- and voltage-dependent currents, and responded to the application of the neurotransmitters acetylcholine and glutamate. The outward current densities were indistinguishable from those in undifferentiated cells. The

inward currents included TTX-sensitive and -resistant Na(+) currents, sustained Ca(2+) currents, and an inwardly rectifying K(+) current. Comparison of the properties of differentiated cells from cHNPCs with neurons obtained from primary fetal cultures (pHNPCs) revealed two major differences: the differentiated cHNPCs did not express embryonic **neural cell** adhesion molecule (E-NCAM) immunoreactivity but did co-express GFAP immunoreactivity. The co-expression of neuronal and **glial** markers was likely due to the growth of cells in serum containing medium as the pHNPCs that were never exposed to serum did express E-NCAM and did not co-express **glial** fibrillary acidic protein (GFAP). The relevance of these results is discussed and compared with results from other neuronal **progenitor** populations and cultured human neuronal cells.

16/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10785769 20341198 PMID: 10877931
Mesencephalic **neural** stem (**progenitor**) cells develop to dopaminergic neurons more strongly in dopamine-depleted striatum than in intact striatum.
Nishino H; Hida H; Takei N; Kumazaki M; Nakajima K; Baba H
Department of Physiology, Nagoya City University Medical School, Japan.
Experimental neurology (UNITED STATES) Jul **2000**, 164 (1) p209-14, ISSN 0014-4886 Journal Code: 0370712
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Epidermal growth factor (EGF)/fibroblast growth factor (FGF)-responsive stem (**progenitor**) cells from embryonic brain have self-renewing and multipotent properties and thus are good candidates for donor cells in **neural** transplantation. However, the survival and differentiation to mature neurons after grafting of stem cells into adult brain are rather poor. We hypothesize that the differentiation of stem cells to mature neurons, such as dopaminergic (DAergic) neurons, is dependent on environmental cues that control the ontogenic development. We compared the survival and differentiation between mesencephalic (MS) and cortical (CTx) stem (**progenitor**) cells, following grafting into bilateral striata of hemiparkinsonian model rats. MS and CTx stem cells were prepared from E12 rats and proliferated in serum-free medium with EGF or basic FGF for 2 weeks. One day after being primed to differentiate, the **cell** suspensions of both origins were grafted into the bilateral striata of adult rats that had unilateral 6-OHDA lesions in the substantia nigra. MS cells differentiated to tyrosine hydroxylase (TH)-positive neurons more strongly in DA-depleted striatum than in intact striatum, and methamphetamine-induced rotation was ameliorated in half of the grafted animals. Rosette-like **cell** aggregation and dysfunction of the blood-brain barrier (BBB) were less in and around the grafts in DA-depleted striatum, suggesting less proliferation and more differentiation of MS stem cells in DA-depleted striatum. Neither TH-positive neurons nor behavioral amelioration were detected following CTx stem (**progenitor**) **cell** transplantation in the striata. Data suggest that the DA-depleted striatum offers a suitable environment for MS stem (**progenitor**) cells to differentiate into mature DAergic neurons. Copyright 2000 Academic Press.

16/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10784409 20345081 PMID: 10884419
Endothelin 3 induces the reversion of melanocytes to glia through a **neural** crest-derived **glial**-melanocytic **progenitor**.

Dupin E; Glavieux C; Vaigot P; Le Douarin N M
Institut d'Embryologie Cellulaire et Moleculaire, Centre National de la Recherche Scientifique (FRE 2160), 49 bis Avenue Belle Gabrielle, 94736 Nogent-sur-Marne Cedex, France.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Jul 5 **2000**, 97 (14) p7882-7, ISSN 0027-8424 Journal Code: 7505876
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Functional signaling of endothelin 3 (ET3) and its receptor B (ETRB) has been shown to be required for the development of **neural** crest (NC)-derived pigment cells in mouse, but the precise role of ET3 is not completely understood. Using the avian embryo as a model, we previously reported that ET3 promotes the survival and proliferation of unipotent melanocyte and bipotent glia-melanocyte precursors in trunk NC cultures. Here we investigated whether, at later stages, embryonic pigment cells respond to ET3. Such a possibility is supported by the previous finding that, in vivo, avian melanocytes express endothelin receptor B2 (ETRB2) during migration and after their differentiation in the skin. We found that in vitro ET3 exerts a dose-dependent stimulation of proliferation and melanogenesis in NC cells that had homed to the epidermis of embryonic quail dorsal skin. Moreover, in clonal cultures of skin-derived pigment cells, ET3 induces rapid **cell** divisions of clonogenic melanocytes that generate a mixed progeny of melanocytes and cells devoid of pigment granules and expressing **glial** markers in more than 40% of the colonies. It can therefore be concluded that ET3 is strongly mitogenic to embryonic pigment cells and able to alter their differentiation program, leading them to recapitulate the **glial**-melanocyte bipotentiality of their NC ancestors.

16/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10714259 20266172 PMID: 10804205
N-CAM binding inhibits the proliferation of hippocampal **progenitor** cells and promotes their differentiation to a neuronal phenotype.
Amoureux M C; Cunningham B A; Edelman G M; Crossin K L
Department of Neurobiology, The Scripps Research Institute, La Jolla, California 92037, USA.
Journal of neuroscience : the official journal of the Society for Neuroscience (UNITED STATES) May 15 **2000**, 20 (10) p3631-40, ISSN 1529-2401 Journal Code: 8102140
Contract/Grant No.: HD 09635; HD; NICHD; HD 16550; HD; NICHD
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
Cell adhesion molecules (CAMs) play important roles during the development of the nervous system. On the basis of our previous observations that binding of the **neural** CAM (N-CAM) inhibits astrocyte proliferation and alters gene expression, we hypothesized that N-CAM may influence the balance between the proliferation and the differentiation of **neural** **progenitor** cells. Rat and mouse hippocampal **progenitor** cells were cultured and showed dependence on basic FGF for proliferation, immunoreactivity for nestin, the presence of limited numbers of differentiated cells, and the ability to generate **glial** cells and neurons under different **culture** conditions. Addition of soluble N-CAM reduced **cell** proliferation in a dose-dependent manner with no evidence of apoptosis. The inhibition of proliferation by N-CAM was accompanied by an induction of differentiation to the neuronal lineage, as indicated by a twofold increase in the

percentage of microtubule-associated protein 2-positive cells even in the presence of mitogenic growth factors. Experiments using hippocampal cells from N-CAM knock-out mice indicated that N-CAM on the **cell** surface is not required for these effects, suggesting the existence of heterophilic signaling. These results support a role for N-CAM and N-CAM ligands in the inhibition of proliferation and the induction of **neural** differentiation of hippocampal **neural progenitor** cells.

16/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10623131 20174858 PMID: 10711716
Retinoic acid produces rod photoreceptor selective apoptosis in developing mammalian retina.
Soderpalm A K; Fox D A; Karlsson J O; van Veen T
Department of Zoology, Goteborg University, Sweden. annika.soderpalm@zool.gu.se
Investigative ophthalmology & visual science (UNITED STATES) Mar **2000**, 41 (3) p937-47, ISSN 0146-0404 Journal Code: 7703701
Contract/Grant No.: ES03183; ES; NIEHS
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed
PURPOSE: All-trans retinoic acid (ATRA) or 9-cis retinoic acid (9CRA), added to dissociated developing **neural** retinal cells, induces **progenitor** cells to adopt the rod **cell**'s fate. Retinoic acid (RA) also produces apoptotic **cell** death in developing tissues. The effects of retinoids on mouse retinal development were examined. METHODS: Retinas were explanted on postnatal day (PN)1 and cultured with or without the retinal pigment epithelium (RPE) attached. Retinas were cultured for 3 weeks in the absence or presence of 100 or 500 nM ATRA or 9CRA. Morphologic development and apoptotic **cell** death were examined using **cell** -specific immunocytochemical markers, the TdT-dUTP terminal nick-end labeling (TUNEL) method, and a caspase assay. RESULTS: Retinal explants, with and without RPE, had similar age-dependent increases in opsin expression. In contrast, explants with RPE had less apoptosis during the first week than retinas without RPE. In explants with RPE, ATRA or 9CRA produced rod-selective apoptotic **cell** death in which 20% to 25% were lost by PN7 with no further loss by PN21. 9CRA-treated explants without RPE had a decreased number of apoptotic cells and a higher number of (rhod)opsin-positive cells at PN3. CONCLUSIONS: Factors in RPE appear to regulate rod apoptosis in developing retina. Retinoids produce rod-selective apoptotic **cell** death during normal rod differentiation. In contrast, retinoids accelerate the expression of opsin in retinas without RPE. These differential effects of RA on rod photoreceptors-apoptosis and differentiation-are similar to those observed in other developing tissues and play an important role in both normal and pathologic development.

16/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10613011 20143690 PMID: 10677254
The Ets domain transcription factor Erm distinguishes rat satellite glia from Schwann cells and is regulated in satellite cells by neuregulin signaling.
Hagedorn L; Paratore C; Brugnoli G; Baert J L; Mercader N; Suter U; Sommer L
Institute of Cell Biology, Swiss Federal Institute of Technology, ETH-Honggerberg, CH-8093, Switzerland.
Developmental biology (UNITED STATES) Mar 1 **2000**, 219 (1)

p44-58, ISSN 0012-1606 Journal Code: 0372762
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

Distinct **glial cell** types of the vertebrate peripheral nervous system (PNS) are derived from the **neural** crest. Here we show that the expression of the Ets domain transcription factor Erm distinguishes satellite glia from Schwann cells beginning early in rat PNS development. In developing dorsal root ganglia (DRG), Erm is present both in presumptive satellite glia and in neurons. In contrast, Erm is not detectable at any developmental stage in Schwann cells in peripheral nerves. In addition, Erm is downregulated in DRG-derived glia adopting Schwann **cell** traits in **culture** . Thus, Erm is the first described transcription factor expressed in satellite glia but not in Schwann cells. In **culture** , the Neuregulin1 (NRG1) isoform GGF2 maintains Erm expression in presumptive satellite cells and reinduces Erm expression in DRG-derived glia but not in Schwann cells from sciatic **nerve** . These data demonstrate that there are intrinsic differences between these **glial** subtypes in their response to NRG1 signaling. In **neural** crest cultures, Erm-positive **progenitor** cells give rise to two distinct **glial** subtypes: Erm-positive, Oct-6-negative satellite glia in response to GGF2, and Erm-negative, Oct-6-positive Schwann cells in the presence of serum and the adenylate cyclase activator forskolin. Thus, Erm-positive **neural** crest-derived **progenitor** cells and presumptive satellite glia are able to acquire Schwann **cell** features. Given the in vivo expression of Erm in peripheral ganglia, we suggest that ganglionic Erm-positive cells may be precursors of Schwann cells. Copyright 2000 Academic Press.

16/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10612988 20153467 PMID: 10686078

Coexpression of nestin in **neural** and **glial** cells in the developing human CNS defined by a human-specific anti-nestin antibody.

Messam C A; Hou J; Major E O
Laboratory of Molecular Medicine, NINDS, Bethesda, Maryland, 20892, USA. messamc@ninds.nih.gov

Experimental neurology (UNITED STATES) Feb **2000**, 161 (2) p585-96, ISSN 0014-4886 Journal Code: 0370712
Document type: Journal Article
Languages: ENGLISH
Main Citation Owner: NLM
Record type: Completed

The presence of the intermediate filament protein nestin has been the predominant marker used to describe stem and **progenitor** cells in the mammalian CNS. In this study, a 998-bp fragment in the 3' region of the nestin mRNA was cloned from human fetal brain cells (HFBC). The nucleotide sequence of the cloned cDNA revealed 21 differences with the previously published human nestin sequence, resulting in 17 amino acid changes. A 150-amino-acid fragment derived from the cloned nestin cDNA was coupled to glutathione S-transferase and used as an immunogen to generate a rabbit polyclonal antiserum that selectively detects human nestin. HFBC that proliferated in response to basic fibroblast growth factor incorporated 5-bromo-2'-deoxyuridine into their nuclei and immunostained for nestin, indicating nestin expression in proliferating CNS **progenitor** cells. In all **cell** cultures, nestin costained with the neuroepithelial **cell** marker vimentin. A small subset of nestin-stained cells (1-2%) immunostained with neuronal marker MAP-2 during the first week and after 4 weeks in **culture**. However, during the first week in **culture**, approximately 10-30% of the total **cell** population of HFBC stained for the **glial cell** marker GFAP, and nearly all coimmunostained for

structural basis underlying the divergent activities of Xnr2 and Xnr3 was analyzed using site-directed mutagenesis. Mutations introduced to the conserved cysteine residues characteristic of the TGFbeta family were found to inactivate Xnr2, but not Xnr3. The most unique feature of Xnr3 is the absence of a conserved cysteine at the C terminus of the protein. This feature distinguishes Xnr3 from other TGFbeta family members, including Xnr2. However, we observed that changing the C terminus of Xnr3 to more closely resemble other TGFbeta family members did not significantly alter its activity, suggesting that other structural features of Xnr3 distinguish its biological activity from Xnr2.

5/3,AB/20 (Item 20 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10030231 99383995
A role for xGCNF in midbrain-hindbrain patterning in Xenopus laevis.
Song K; Takemaru KI; Moon RT
Department of Pharmacology, University of Washington School of Medicine, Seattle, Washington 98195, USA.
Developmental biology (UNITED STATES) Sep 1 1999, 213 (1) p170-9, ISSN 0012-1606 Journal Code: E7T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Cells in the presumptive **neural** ectoderm of Xenopus are committed to **neural** fate through a process called **neural** induction, which may involve proteins that antagonize **BMP** signaling pathways. To identify genes that are induced by the **BMP** antagonists and that may be involved in subsequent **neural** patterning, we used a suppression PCR-based subtraction screen. Here we investigate the prospective activities and functions of one of the genes, a nuclear orphan receptor previously described as xGCNF. In animal cap assays, xGCNF synergizes with ectopic **chordin** to induce the midbrain-hindbrain marker engrailed-2 (En-2). In Keller explants, which rely on endogenous factors for **neural** induction, similar increases in En-2 are observed. Expression in embryos of a dominant interfering form of xGCNF reduces the expression of endogenous En-2 and Krox-20. These gain-of-function and prospective loss-of-function experiments, taken with the observation that xGCNF is expressed in the early **neural** plate and is elevated in the prospective midbrain-hindbrain region, which subsequently expresses En-2, suggest that xGCNF may play a role in regulating En-2 and thus midbrain-hindbrain identity. Copyright 1999 Academic Press.

5/3,AB/21 (Item 21 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10029841 99396700
Xenopus GDF6, a new antagonist of **noggin** and a partner of BMPs.
Chang C; Hemmati-Brivanlou A
Department of Molecular Embryology, The Rockefeller University, New York, NY 10021, USA.
Development (ENGLAND) Aug 1999, 126 (15) p3347-57, ISSN 0950-1991 Journal Code: ECW
Contract/Grant No.: HD 32105-01, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In Xenopus, ectodermal cell fates are determined by antagonistic interaction between the **BMP** subfamily of TGF-(beta) ligands and the organizer-specific secreted factors (e.g. **noggin**, **chordin** and **follistatin**). Inhibition of **BMP** function by these factors can convert cells from an epidermal to a **neural** cell fate. In this study, we report that GDF6, a new member of the Xenopus TGF-(beta) family, can

function in antagonistic interaction with **neural** inducers. GDF6 induces epide[redacted] and inhibits **neural** tissue[redacted] dissociated cells, and this activity is blocked by the presence of **noggin**. We demonstrate that GDF6 binds directly to the **neural** inducer **noggin**. Furthermore, we find that GDF6 and BMP2 can form heterodimers and the process seems to require cotranslation of the proteins in the same cells. In normal embryos, GDF6 and BMP2 are coexpressed in several places, including the edge of the **neural** plate at early neurula stages, suggesting that GDF6 may synergize with BMPs to regulate patterning of the ectoderm. Our data show for the first time that **noggin** can bind directly to and inhibit another TGF-(beta) family member: GDF6. In addition, **BMP** and GDF6 heterodimers may play an important role in vivo to regulate cell fate determination and patterning.

5/3,AB/22 (Item 22 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10018725 99345945
Mesoderm patterning and somite formation during node regression: differential effects of **chordin** and **noggin**.
Streit A; Stern CD
Department of Genetics and Development, Columbia University, 701 West 168th Street #1602, New York, NY 10032, USA.
Mechanisms of development (IRELAND) Jul 1999, 85 (1-2) p85-96, ISSN 0925-4773 Journal Code: AXF
Contract/Grant No.: HD31942, HD, NICHD; GM53456, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In Xenopus, one of the properties defining Spemann's organizer is its ability to dorsalise the mesoderm. When placed ajacent to prospective lateral/ventral mesoderm (blood, mesenchyme), the organizer causes these cells to adopt a more axial/dorsal fate (muscle). It seems likely that a similar property patterns the primitive streak of higher vertebrate embryos, but this has not yet been demonstrated clearly. Using quail/chick chimaeras and a panel of molecular markers, we show that Hensen's node (the amniote organizer) can induce posterior primitive streak (prospective lateral plate) to form somites (but not notochord) at the early neurula stage. We tested two **BMP** antagonists, **noggin** and **chordin** (both of which are expressed in the organizer), for their ability to generate somites and intermediate mesoderm from posterior streak, and find that **noggin**, but not **chordin**, can do this. Conversely, earlier in development, **chordin** can induce an ectopic primitive streak much more effectively than **noggin**, while neither **BMP** antagonist can induce **neural** tissue from extraembryonic epiblast. Neurulation is accompanied by regression of the node, which brings the prospective somite territory into a region expressing **BMP**-2, -4 and -7. One function of **noggin** at this stage may be to protect the prospective somite cells from the inhibitory action of BMPs. Our results suggest that the two **BMP** antagonists, **noggin** and **chordin**, may serve different functions during early stages of amniote development.

5/3,AB/23 (Item 23 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10007260 99365368
Multiple roles of bone morphogenetic protein signaling in the regulation of cortical cell number and phenotype.
Mabie PC; Mehler MF; Kessler JA
Departments of Neurology and Neuroscience and the R. F. Kennedy Center for Research in Mental Retardation and Human Development, Albert Einstein College of Medicine, Bronx, New York 10461, USA.

DIALOG(R)File 155:MEDLINE(R)
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10233357 20069485
Wnt signaling in Xenopus embryos inhibits bmp4 expression and activates **neural** development.
Baker JC; Beddington RS; Harland RM
Department of Molecular and Cell Biology, University of California, Berkeley, California 94720, USA.
Genes & development (UNITED STATES) Dec 1 1999, 13 (23) p3149-59, ISSN 0890-9369 Journal Code: FN3
Contract/Grant No.: GM42341, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We report a new role for Wnt signaling in the vertebrate embryo: the induction of **neural** tissue from ectoderm. Early expression of mouse wnt8, Xwnt8, beta-catenin, or dominant-negative GSK3 induces the expression of **neural** -specific markers and inhibits the expression of Bmp4 in Xenopus ectoderm. We show that Wnt8, but not the **BMP** antagonist **Noggin** , can inhibit Bmp4 expression at early gastrula stages. Furthermore, inhibition of beta-catenin activity in the **neural** ectoderm of whole embryos by a truncated TCF results in a decrease in **neural** development. Therefore, we suggest that a cleavage-stage Wnt signal normally contributes to an early repression of Bmp4 on the dorsal side of the embryo and sensitizes the ectoderm to respond to **neural** inducing signals from the organizer. The Wnt targets Xnr3 and siamois have been shown previously to have neuralizing activity when overexpressed. However, antagonists of Wnt signaling, dnXwnt8 and Nxfrz8, inhibit Wnt-mediated Xnr3 and siamois induction, but not **neural** induction, suggesting an alternative mechanism for **Bmp** repression and neuralization. Conversely, dnTCF blocks both Wnt-mediated Xnr3 and **neural** induction, suggesting that both pathways require this transcription factor.

5/3,AB/14 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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10200601 99370092
BMP-4 inhibits **neural** differentiation of murine embryonic stem cells.
Finley MF; Devata S; Huettner JE
Department of Cell Biology and Physiology and Program in Neuroscience, Washington University Medical School, 660 South Euclid Avenue, St. Louis, Missouri 63110, USA.
Journal of neurobiology (UNITED STATES) Sep 5 1999, 40 (3) p271-87, ISSN 0022-3034 Journal Code: JAM
Contract/Grant No.: NS30888, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Members of the transforming growth factor-beta superfamily, including bone morphogenetic protein 4 (**BMP** -4), have been implicated as regulators of neuronal and glial differentiation. To test for a possible role of **BMP**-4 in early mammalian **neural** specification, we examined its effect on neurogenesis in aggregate cultures of mouse embryonic stem (ES) cells. Compared to control aggregates, in which up to 20% of the cells acquired immunoreactivity for the **neuron**-specific antibody TuJ1, aggregates maintained for 8 days in serum-free medium containing **BMP**-4 generated 5- to 10-fold fewer neurons. The action of **BMP** -4 was dose dependent and restricted to the fifth through eighth day in suspension. In addition to the reduction in neurons, we observed that ES cell cultures exposed to **BMP**-4 contained fewer cells that were immunoreactive for glial fibrillary acidic protein or the HNK-1 **neural** antigen. Furthermore, under phase contrast, cultures prepared

from **BMP** -4-treated aggregates contained a significant proportion of nonneuronal cells with a characteristic flat, elongated morphology. These cells were immunoreactive for antibodies to the intermediate filament protein vimentin; they were rare or absent in control cultures. Treatment with **BMP** -4 enhanced the expression of the early mesodermal genes brachyury and tbx6 but had relatively little effect on total cell number or cell death. Coapplication of the **BMP**-4 antagonist **noggin** counteracted the effect of exogenous **BMP**-4, but **noggin** alone had no effect on neuralization in either the absence or presence of retinoids. Collectively, our results suggest that **BMP**-4 can overcome the neuralizing action of retinoic acid to enhance mesodermal differentiation of murine ES cells.

5/3,AB/15 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10193622 20032758
Noggin is a mesenchymally derived stimulator of hair-follicle induction.
Botchkarev VA; Botchkareva NV; Roth W; Nakamura M; Chen LH; Herzog W; Lindner G; McMahon JA; Peters C; Lauster R; McMahon AP; Paus R
Department of Dermatology, Charite, Humboldt-University Berlin, Germany.
Nature cell biology (ENGLAND) Jul 1999, 1 (3) p158-64, ISSN 1465-7392 Journal Code: DIQ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The induction of developmental structures derived from the ectoderm, such as the **neural** tube or tooth, occurs through neutralization of the inhibitory activity of members of the bone-morphogenetic protein (**BMP**) family by **BMP** antagonists. Here we show that, during hair-follicle development, the **neural** inducer and **BMP**-neutralizing protein **Noggin** is expressed in the follicular mesenchyme, that **noggin**-knockout mice show significant retardation of hair-follicle induction, and that **Noggin** neutralizes the inhibitory action of **BMP**-4 and stimulates hair-follicle induction in embryonic skin organ culture. As a crucial mesenchymal signal that stimulates hair-follicle induction, **Noggin** operates through antagonistic interactions with **BMP**-4, which result in upregulation of the transcription factor Lef-1 and the cell-adhesion molecule NCAM, as well as through BMP4-independent downregulation of the 75 kD neurotrophin receptor in the developing hair follicle.

5/3,AB/16 (Item 16 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10158831 99456774
Flik, a chick **follistatin**-related gene, functions in gastrular dorsalisation/**neural** induction and in subsequent maintenance of midline Sonic hedgehog signalling.
Towers P; Patel K; Withington S; Isaac A; Cooke J
Division of Developmental Neurobiology, National Institute for Medical Research, The Ridgeway, Mill Hill, London, NW7 1AA, United Kingdom.
Developmental biology (UNITED STATES) Oct 15 1999, 214 (2) p298-317, ISSN 0012-1606 Journal Code: E7T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have targetted the chick gene Flik with antisense oligodeoxynucleotide treatment at gastrular stages, when it is expressed in organiser-derived structures of the midline (K. Patel et al., 1996, Dev. Biol. 178, 327-342). A specific syndrome of deficient axial patterning and holoprosencephaly is produced. Most aspects of this syndrome can be understood as due to

attenuation of dorsalising and **neural** -inducing signals during gastrulation, followed by failure to maint[illegible] the later signals from chordamesoderm/**neural** midline that pattern the mesodermal and **neural** cross sections during subsequent stages. Anatomical effects are first apparent at early neurula stages and correspond with what might be expected from a reduced counteraction of the ventralising Bone morphogenetic protein (**BMP**) pathway at the earlier stages, coupled with inadequate Sonic hedgehog (Shh) signalling subsequently. Delay in the clearing of **BMP**-4 RNA expression from the presumptive **neural** region at gastrulation is indeed seen, though **chordin** RNA expression within organiser derivatives remains normal. Subsequently, specific attenuation of chordamesoderm and **neural** midline Shh expression is observed. Brief preincubation of stage 4 chick blastoderms in supernatant from Xenopus oocytes that have been injected with Flik RNA prolongs and enhances the competence of their peripheral epiblast to respond to **neural** inductive signals from grafted Hensen's nodes. This effect specifically mimics that recently observed using microg/ml solutions of recombinant **Follistatin** (D. J. Connolly et al., 1999, Int. J. Dev. Biol., in press), further suggesting that Flik protein might act in vivo by somehow modulating activity of signalling pathways through **BMP** or other TGFbeta-related ligands. We discuss the significance of the observations in relation to recent ideas about **neural** induction, about possible redundancy in gene action, and about subsequent patterning of the axial cross section, suggesting that a Flik function in autocrine/paracrine maintenance of later midline Shh signalling represents a role of the gene separate from that in primary dorsalisation/**neural** induction. Copyright 1999 Academic Press.

5/3,AB/17 (Item 17 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10129830 99238235
Noggin upregulates Fos expression by a calcium-mediated pathway in amphibian embryos.
Leclerc C; Duprat AM; Moreau M
Centre de Biologie du Developpement, UMR 5547, Universite Paul Sabatier, Toulouse, France.
Development, growth & differentiation (JAPAN) Apr 1999, 41 (2) p227-38
, ISSN 0012-1592 Journal Code: E7Y
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In amphibia, **noggin**, one of the **neural** inducers expressed in the Spemann organizer, acts by neutralizing the effects of bone morphogenetic protein-4 (**BMP**-4). It is shown that **noggin** is able to activate L-type calcium channels. The fos proto-oncogene is known to be induced within minutes by calcium signaling. Here it is reported that in animal cap explants of the amphibian Pleurodeles waltl, **noggin** can induce upregulation of a FOS-related protein in a calcium-dependent manner. Specific inhibition of the dihydropyridine sensitive L-type calcium channels blocked both calcium influx and the induction of FOS-related protein. When animal cap explants were treated with caffeine in order to release calcium from an internal store or with a specific agonist of the L-type calcium channels, FOS-related protein could be detected in cell nuclei by 5 or 15 min, respectively. Additionally, the calcium calmodulin kinase inhibitor. KN62, could block the upregulation of FOS-related protein induced by agents that increased intracellular calcium ([Ca2+]i). The present results suggest that transcription factors from the FOS family are downstream targets of **neural** inducer **noggin**.

5/3,AB/18 (Item 18 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10118452 99059179
DAN is a secreted glycoprotein related to Xenopus cerberus.
Stanley E; Biben C; Kotecha S; Fabri L; Tajbakhsh S; Wang CC; Hatzistavrou T; Roberts B; Drinkwater C; Lah M; Buckingham M; Hilton D; Nash A; Mohun T; Harvey RP
The Walter and Eliza Hall Institute of Medical Research, Post Office, Royal Melbourne Hospital, Parkville 3050, Australia.
Mechanisms of development (IRELAND) Oct 1998, 77 (2) p173-84, ISSN 0925-4773 Journal Code: AXF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We report that DAN, a potential cell cycle regulator and tumour suppressor, is a secreted glycoprotein related to Xenopus cerberus. DAN, cerberus, its mouse relative Cer-1/cer-1/Cerberus-like/Cerr1, and the recently described factor DRM/**Gremlin**, appear to be members of the cystine knot superfamily, which includes TGFbetas and BMPs. Like cerberus and mCer-1, DAN-induced cement glands as well as markers of anterior **neural** tissue and endoderm in Xenopus animal cap assays, features of **BMP** signalling blockade. During mouse embryogenesis, Dan was expressed from E8.5 in cranial mesenchyme and somites, then later in limb and facial mesenchyme. The pattern in somites was highly dynamic, with transcripts initially localized to the caudal half of the nascent epithelial somite, then, after maturation, to sclerotomal cells adjacent to the **neural** tube. Dan was also expressed in the developing myotome. The expression domains include sites in which **BMP** inhibition is known to be important for development. Thus, DAN appears to be a secreted factor belonging to the cystine knot superfamily, and one of a growing number of antagonists acting to modulate **BMP** signalling during development.

5/3,AB/19 (Item 19 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

10073891 97178983
Direct **neural** induction and selective inhibition of mesoderm and epidermis inducers by Xnr3.
Hansen CS; Marion CD; Steele K; George S; Smith WC
Department of Molecular, Cellular and Developmental Biology, University of California, Santa Barbara 93106, USA.
Development (ENGLAND) Jan 1997, 124 (2) p483-92, ISSN 0950-1991 Journal Code: ECW
Contract/Grant No.: GM52835, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
During gastrulation in amphibians, secreted factors from Spemann's organizer act on dorsal ectoderm to induce the central nervous system. A number of secreted factors produced by Spemann's organizer have recently been identified. The TGFbeta family member Xnr3 is similar in amino acid sequence to the mouse factor nodal and is expressed in a restricted group of cells in the superficial layer of Spemann's organizer. Xnr3, unlike the related factors nodal, Xnr1 and Xnr2, lacks mesoderm-inducing activity. We report here that Xnr3 can directly induce **neural** tissue in Xenopus ectoderm explants (animal caps). Injection of animal caps with either Xnr3 RNA or plasmids induces the expression of the pan-**neural** genes NCAM and nrp1, as well as the anterior **neural** marker Cpl1. A growing body of evidence suggests that **neural** induction in Xenopus proceeds as the default in the absence of epidermis inducers. The best candidates for the endogenous epidermis inducers are **BMP**-4 and **BMP**-7. The **neural** inducing activity of Xnr3 can be inhibited by overexpression of **BMP**-4, as has been observed with the **neural** inducers **noggin**, **chordin** and **follistatin**. Furthermore, Xnr3 can block mesoderm induction by **BMP**-4 and activin, but not by Xnr2. The

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ISSN 0270-6474 Journal Code: JDF
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Members of the bone morphogenetic protein (**BMP**) family have been implicated in multiple aspects of **neural** development in both the CNS and peripheral nervous system. **BMP** ligands and receptors, as well as the **BMP** antagonist **noggin** , are expressed in the developing cerebral cortex, making the BMPs likely candidates for regulating cortical development. To define the role of these factors in the developing cerebral cortex, we examined the effects of BMP2 and BMP4 on cortical cells in vitro. Cells were cultured from embryonic day 13 (E13) and E16 rat cerebral cortex in the absence or presence of different concentrations of fibroblast growth factor 2, a known regulator of cortical cell proliferation and differentiation. At E13, the BMPs promoted cell death and inhibited proliferation of cortical ventricular zone cells, resulting in the generation of fewer neurons and no glia. At E16, the effects of the BMPs were more complex. Concentrations of BMP2 in the range of 1-10 ng/ml promoted neuronal and astroglial differentiation and inhibited oligodendroglial differentiation, whereas 100 ng/ml BMP2 promoted cell death and inhibited proliferation. Addition of the **BMP** antagonist **noggin** promoted oligodendrogliogenesis in vitro, demonstrating that endogenous **BMP** signaling influences the differentiation of cortical cells in vitro. The distribution of BMP2 and **noggin** within the developing cortex suggests that local concentrations of ligands and antagonists define gradients of **BMP** signaling during corticogenesis. Together, these results support the hypothesis that the BMPs and their antagonist **noggin** co-regulate cortical cell fate and morphogenesis.

5/3,AB/24 (Item 24 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09999255 99350216

Animal-vegetal asymmetries influence the earliest steps in retina fate commitment in Xenopus.

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Developmental biology (UNITED STATES) Aug 1 1999, 212 (1) p25-41,
ISSN 0012-1606 Journal Code: E7T
Contract/Grant No.: F32 EY06649, EY, NEI; R01 EY10096, EY, NEI
Languages: ENGLISH
Document type: JOURNAL ARTICLE

An individual retina descends from a restricted and invariant group of nine animal blastomeres at the 32-cell stage. We tested which molecular signaling pathways are responsible for the competence of animal blastomeres to contribute to the retina. Inactivation of activin/Vg1 or fibroblast growth factor (FGF) signaling by expression of dominant-negative receptors does not prevent an animal blastomere from contributing to the retina. However, increasing bone morphogenetic protein (**BMP**) signaling in the retina-producing blastomeres significantly reduces their contribution. Conversely, reducing **BMP** signaling by expression of a dominant-negative **BMP** receptor or **Noggin** allows other animal blastomeres to contribute to the retina. Thus, the initial step in the retinal lineage is regulated by position within the **BMP/Noggin** field of epidermal versus **neural** induction. Vegetal tier blastomeres, in contrast, cannot contribute to the retina even when given access to the appropriate position and signaling fields by transplantation to the dorsal animal pole. We tested whether expression of molecules within the mesoderm inducing (activin, FGF), mesoderm-modifying (Wnt), or **neural**-inducing (**BMP**, **Noggin**) pathways impart a retinal fate on vegetal cell descendants. None of these, several of which induce

secondary head structures, caused vegetal cells to contribute to retina. This was true even if the injected blastomeres were transplanted to the dorsal animal pole. Two pathways that specifically induce head tissues also were investigated. The simultaneous blockade of Wnt and **BMP** signaling, which results in the formation of a complete secondary axis with head and eyes, did not cause the vegetal clone to give rise to retina. However, Cerberus, a secreted protein that also induces an ectopic head with eyes, redirected vegetal progeny into the retina. These experiments indicate that vegetal blastomere incompetence to express a retinal fate is not due to a lack of components of known signaling pathways, but relies on a specific pathway of head induction. Copyright 1999 Academic Press.

5/3,AB/25 (Item 25 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09991336 99307076
The role of tolloid/mini fin in dorsoventral pattern formation of the zebrafish embryo.
Connors SA; Trout J; Ekker M; Mullins MC
University of Pennsylvania School of Medicine, Department of Cell and Developmental Biology, 421 Curie Blvd., Philadelphia, PA 19104-6058, USA. mullins@mail.med.upenn.edu
Development (ENGLAND) Jun 1999, 126 (14) p3119-30, ISSN 0950-1991
Journal Code: ECW
Contract/Grant No.: RO1-GM56326, GM, NIGMS; T32 HD07305, HD, NICHD; T32 HD07516 01, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A highly conserved TGF-&bgr; signaling pathway is involved in the establishment of the dorsoventral axis of the vertebrate embryo. Specifically, Bone Morphogenetic Proteins (Bmps) pattern ventral tissues of the embryo while inhibitors of Bmps, such as **Chordin**, **Noggin** and **Follistatin**, are implicated in dorsal mesodermal and **neural** development. We investigated the role of Tolloid, a metalloprotease that can cleave **Chordin** and increase **Bmp** activity, in patterning the dorsoventral axis of the zebrafish embryo. Injection of tolloid mRNA into six dorsalized mutants rescued only one of these mutants, mini fin. Through chromosomal mapping, linkage and cDNA sequence analysis of several mini fin alleles, we demonstrate that mini fin encodes the tolloid gene. Characterization of the mini fin mutant phenotype reveals that Mini fin/Tolloid activity is required for patterning ventral tissues of the tail: the ventral fin, and the ventroposterior somites and vasculature. Gene expression studies show that mfn mutants exhibit reduced expression of ventrally restricted markers at the end of gastrulation, suggesting that the loss of ventral tail tissues is caused by a dorsalization occurring at the end of gastrulation. Based on the mini fin mutant phenotype and the expression of tolloid, we propose that Mini fin/Tolloid modifes the **Bmp** activity gradient at the end of gastrulation, when the ventralmost marginal cells of the embryo are in close proximity to the dorsal **Chordin**-expressing cells. At this time, unimpeded **Chordin** may diffuse to the most ventral marginal regions and inhibit high **Bmp** activity levels. In the presence of Mini fin/Tolloid, however, **Chordin** activity would be negatively modulated through proteolytic cleavage, thereby increasing **Bmp** signaling activity. This extracellular mechanism is amplified by an autoregulatory loop for **bmp** gene expression.

5/3,AB/26 (Item 26 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09974047 99284518

recently been reported that calmodulin interacts with the N-terminal domain of Smad proteins. We demonstrate that the ventralizing activity of hSmad1 and hSmad1(N) is markedly inhibited by calmodulin. Thus, calmodulin acts as a Smad1 inhibitor. A model is proposed to accomodate these findings.

5/3,AB/28 (Item 28 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09917331 99195793
A Meis family protein caudalizes **neural** cell fates in Xenopus.
Salzberg A; Elias S; Nachaliel N; Bonstein L; Henig C; Frank D
Department of Biochemistry, Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel.
Mechanisms of development (IRELAND) Jan 1999, 80 (1) p3-13, ISSN 0925-4773 Journal Code: AXF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A homologue of the Drosophila homothorax (hth) gene, Xenopus Meis3 (XMeis3), was cloned from Xenopus laevis. XMeis3 is expressed in a single stripe of cells in the early **neural** plate stage. By late neurula, the gene is expressed predominantly in rhombomeres two, three and four, and in the anterior spinal cord. Ectopic expression of RNA encoding XMeis3 protein causes anterior **neural** truncations with a concomitant expansion of hindbrain and spinal cord. Ectopic XMeis3 expression inhibits anterior **neural** induction in neuralized animal cap ectoderm explants without perturbing induction of pan-**neural** markers. In naive animal cap ectoderm, ectopic XMeis3 expression activates transcription of the posteriorly expressed **neural** markers, but not pan-**neural** markers. These results suggest that caudalizing proteins, such as XMeis3, can alter A-P patterning in the nervous system in the absence of **neural** induction. Regionally expressed proteins like XMeis3 could be required to overcome anterior signals and to specify posterior cell fates along the A-P axis.

5/3,AB/29 (Item 29 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09876823 99187893
Neural induction. A bird's eye view.
Streit A; Stern CD
Department of Genetics and Development, College of Physicians and Surgeons of Columbia University, New York, NY 10032, USA. ace3@columbia.edu
Trends in genetics (ENGLAND) Jan 1999, 15 (1) p20-4, ISSN 0168-9525 Journal Code: WEK
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Since the discovery of the phenomenon of **neural** induction by Spemann and Mangold in 1924, considerable effort has been invested in identifying the signals produced by the organizer that are responsible for diverting the fate of cells from epidermal to **neural**. Substantial progress has been made only recently by the finding in amphibians that BMP4 is a **neural** inhibitor and epidermal inducer, and that endogenous antagonists of BMPs are secreted by the organizer. However, recent results in the chick point to the existence of other, upstream events required before **BMP** inhibition stabilizes **neural** fates. Here we take a critical view of the evidence for and against the view that **BMP** inhibition is a sufficient trigger for **neural** induction in different vertebrates.

5/3,AB/30 (Item 30 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09873356 99177155
A novel **BMP** expressed in developing mouse limb, spinal cord, and tail bud is a potent mesoderm inducer in Xenopus embryos.
Gamer LW; Wolfman NM; Celeste AJ; Hattersley G; Hewick R; Rosen V
Genetics Institute, Inc., 87 Cambridge Park Drive, Cambridge, Massachusetts 02140, USA. lgamer@genetics.com
Developmental biology (UNITED STATES) Apr 1 1999, 208 (1) p222-32, ISSN 0012-1606 Journal Code: E7T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The bone morphogenetic proteins (BMPs) play critical roles in patterning the early embryo and in the development of many organs and tissues. We have identified a new member of this multifunctional gene family, **BMP**-11, which is most closely related to GDF-8/myostatin. During mouse embryogenesis, **BMP** -11 is first detected at 9.5 dpc in the tail bud with expression becoming stronger as development proceeds. At 10.0 dpc, **BMP** -11 is expressed in the distal and posterior region of the limb bud and later localizes to the mesenchyme between the skeletal elements. **BMP** -11 is also expressed in the developing nervous system, in the dorsal root ganglia, and dorsal lateral region of the spinal cord. To assess the biological activity of **BMP**-11, we tested the protein in the Xenopus ectodermal explant (animal cap) assay. **BMP**-11 induced axial mesodermal tissue (muscle and notochord) in a dose-dependent fashion. At higher concentrations, **BMP**-11 also induced **neural** tissue. Interestingly, the activin antagonist, **follistatin**, but not **noggin**, an antagonist of BMPs 2 and 4, inhibited **BMP**-11 activity on animal caps. Our data suggest that in Xenopus embryos, **BMP**-11 acts more like activin, inducing dorsal mesoderm and **neural** tissue, and less like other family members such as BMPs 2, 4, and 7, which are ventralizing and anti-neuralizing signals. Taken together, these data suggest that during vertebrate embryogenesis, **BMP**-11 plays a unique role in patterning both mesodermal and **neural** tissues.

5/3,AB/31 (Item 31 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09833040 99112969
Head induction in the chick by primitive endoderm of mammalian, but not avian origin.
Knoetgen H; Viebahn C; Kessel M
Max-Planck-Institut fur biophysikalische Chemie, Abteilung Molekulare Zellbiologie, Am Fassberg, D-37077 Gottingen, Germany.
Development (ENGLAND) Feb 1999, 126 (4) p815-25, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Different types of endoderm, including primitive, definitive and mesendoderm, play a role in the induction and patterning of the vertebrate head. We have studied the formation of the anterior **neural** plate in chick embryos using the homeobox gene GANF as a marker. GANF is first expressed after mesendoderm ingression from Hensen's node. We found that, after transplantation, neither the avian hypoblast nor the anterior definitive endoderm is capable of GANF induction, whereas the mesendoderm (young head process, prechordal plate) exhibits a strong inductive potential. GANF induction cannot be separated from the formation of a proper **neural** plate, which requires an intact lower layer and the presence of the prechordal mesendoderm. It is inhibited by BMP4 and promoted by the presence of the **BMP** antagonist **Noggin**. In order

to investigate the inductive potential of the mammalian visceral endoderm, we used rabbit embryos which, in contrast to mouse embryos, allow the morphological recognition of the prospective anterior pole in the living, pre-primitive-streak embryo. The anterior visceral endoderm from such rabbit embryos induced neuralization and independent, ectopic GANF expression domains in the area pellucida or the area opaca of chick hosts. Thus, the signals for head induction reside in the anterior visceral endoderm of mammals whereas, in birds and amphibia, they reside in the prechordal mesendoderm, indicating a heterochronic shift of the head inductive capacity during the evolution of mammalia.

5/3,AB/32 (Item 32 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09808453 99065509
Differential patterning of ventral midline cells by axial mesoderm is regulated by BMP7 and **chordin**.
Dale K; Sattar N; Heemskerk J; Clarke JD; Placzek M; Dodd J
Department of Physiology and Cellular Biophysics and Center for Neurobiology and Behavior, Columbia University, New York, USA.
Development (ENGLAND) Jan 1999, 126 (2) p397-408, ISSN 0950-1991
Journal Code: ECW
Contract/Grant No.: NS30532, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Ventral midline cells in the **neural** tube have distinct properties at different rostrocaudal levels, apparently in response to differential signalling by axial mesoderm. Floor plate cells are induced by sonic hedgehog (SHH) secreted from the notochord whereas ventral midline cells of the rostral diencephalon (RDVM cells) appear to be induced by the dual actions of SHH and bone morphogenetic protein 7 (BMP7) from prechordal mesoderm. We have examined the cellular and molecular events that govern the program of differentiation of RDVM cells under the influence of the axial mesoderm. By fate mapping, we show that prospective RDVM cells migrate rostrally within the **neural** plate, passing over rostral notochord before establishing register with prechordal mesoderm at stage 7. Despite the co-expression of SHH and BMP7 by rostral notochord, prospective RDVM cells appear to be specified initially as caudal ventral midline neurectodermal cells and to acquire RDVM properties only at stage 7. We provide evidence that the signalling properties of axial mesoderm over this period are regulated by the **BMP** antagonist, **chordin**. **Chordin** is expressed throughout the axial mesoderm as it extends, but is downregulated in prechordal mesoderm coincident with the onset of RDVM cell differentiation. Addition of **chordin** to conjugate explant cultures of prechordal mesoderm and **neural** tissue prevents the rostralization of ventral midline cells by prechordal mesoderm. **Chordin** may thus act to refine the patterning of the ventral midline along the rostrocaudal axis.

5/3,AB/33 (Item 33 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09784493 99030283
XBF-2 is a transcriptional repressor that converts ectoderm into **neural** tissue.
Mariani FV; Harland RM
Department of Molecular and Cell Biology, University of California, Berkeley, CA 94720, USA.
Development (ENGLAND) Dec 1998, 125 (24) p5019-31, ISSN 0950-1991
Journal Code: ECW
Contract/Grant No.: GM 42341, GM, NIGMS

Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have identified Xenopus Brain Factor 2 (XBF-2) as a potent neuralizing activity in an expression cloning screen. In ectodermal explants, XBF-2 converts cells from an epidermal to a **neural** fate. Such explants contain neurons with distinct axonal profiles and express both anterior and posterior central nervous system (CNS) markers. In striking contrast to X-ngnR-1a or X-NeuroD, ectopic expression of XBF-2 in Xenopus embryos results in an expansion of the **neural** plate to the ventral midline. The enlarged **neural** plate consists predominantly of undifferentiated neurons. XBF-2 lies downstream of the **BMP** antagonists **noggin**, cerberus, and **gremlin** since ectodermal explants expressing these molecules exhibit strong expression of XBF-2. While XBF-2 does not upregulate the expression of secreted **neural** inducers, it downregulates the transcription of **BMP**-4, an epidermal inducer. We show that XBF-2 acts as a transcriptional repressor and that its effects can be phenocopied with either the engrailed or hairy repressor domain fused to the XBF-2 DNA-binding domain. A fusion of the DNA-binding domain to the activator domain of VP16 blocks the effects of XBF-2 and prevents **neural** plate development in the embryo. This provides evidence that a transcriptional repressor can affect both regional **neural** development and neurogenesis in vertebrates.

5/3,AB/34 (Item 34 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09784485 99030273
Effects of Shh and **Noggin** on **neural** crest formation demonstrate that **BMP** is required in the **neural** tube but not ectoderm.
Selleck MA; Garcia-Castro MI; Artinger KB; Bronner-Fraser M
Division of Biology and Beckman Institute, Pasadena, CA 91125, USA.
Development (ENGLAND) Dec 1998, 125 (24) p4919-30, ISSN 0950-1991 Journal Code: ECW
Contract/Grant No.: NS34671, NS, NINDS; NS36585, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
To define the timing of **neural** crest formation, we challenged the fate of presumptive **neural** crest cells by grafting notochords, Sonic Hedgehog- (Shh) or **Noggin** -secreting cells at different stages of neurulation in chick embryos. Notochords or Shh-secreting cells are able to prevent **neural** crest formation at open **neural** plate levels, as assayed by DiI-labeling and expression of the transcription factor, Slug, suggesting that **neural** crest cells are not committed to their fate at this time. In contrast, the **BMP** signaling antagonist, **Noggin**, does not repress **neural** crest formation at the open **neural** plate stage, but does so if injected into the lumen of the closing **neural** tube. The period of **Noggin** sensitivity corresponds to the time when BMPs are expressed in the dorsal **neural** tube but are down-regulated in the non-**neural** ectoderm. To confirm the timing of **neural** crest formation, Shh or **Noggin** were added to **neural** folds at defined times in culture. Shh inhibits **neural** crest production at early stages (0-5 hours in culture), whereas **Noggin** exerts an effect on **neural** crest production only later (5-10 hours in culture). Our results suggest three phases of neurulation that relate to **neural** crest formation: (1) an initial **BMP** -independent phase that can be prevented by Shh-mediated signals from the notochord; (2) an intermediate **BMP**-dependent phase around the time of **neural** tube closure, when **BMP**-4 is expressed in the dorsal **neural** tube; and (3) a later pre-migratory phase which is refractory to exogenous Shh and **Noggin**.

5/3,AB/35 (Item 35 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09747813 99061953
Mitogen-activated protein kinase and **neural** specification in Xenopus.
Uzgare AR; Uzman JA; El-Hodiri HM; Sater AK
Department of Biology, University of Houston, Houston, TX 77204-5513, USA.
Proceedings of the National Academy of Sciences of the United States of America (UNITED STATES) Dec 8 1998, 95 (25) p14833-8, ISSN 0027-8424 Journal Code: PV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have investigated the activity and function of mitogen-activated protein kinase (MAPK) during **neural** specification in Xenopus. Ectodermal MAPK activity increased between late blastula and midgastrula stages. At midgastrula, MAPK activity in both newly induced **neural** ectoderm and ectoderm overexpressing the anterior **neural** inducer **noggin** was 5-fold higher than in uninduced ectoderm. Overexpression of MAPK phosphatase-1 (MKP-1) in ectoderm inhibited MAPK activity and prevented neurectoderm-specific gene expression when the ectoderm was recombined with dorsal mesoderm or treated with fibroblast growth factor (FGF). Neurectoderm-specific gene expression was observed, however, in ectoderm overexpressing both **noggin** and MKP-1. To evaluate the role of MAPK in posterior regionalization, ectodermal isolates were treated with increasing concentrations of FGF and assayed for MAPK activity and neurectoderm-specific gene expression. Although induction of posterior **neural** ectoderm by FGF was accompanied by an elevation of MAPK activity, relative MAPK activity associated with posterior **neural** fate was no higher than that of ectoderm specified to adopt an anterior **neural** fate. Thus, increasingly posterior **neural** fates are not correlated with quantitative increases in MAPK activity. Because MAPK has been shown to down-regulate Smad1, MAPK may disrupt bone morphogenetic protein 4 (**BMP**-4) signaling during **neural** specification. Our results suggest that MAPK plays an essential role in the establishment of **neural** fate in vivo.

5/3,AB/36 (Item 36 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09698365 98440832
Transcriptional regulation of **BMP**-4 in the Xenopus embryo: analysis of genomic **BMP**-4 and its promoter.
Kim J; Ault KT; Chen HD; Xu RH; Roh DH; Lin MC; Park MJ; Kung HF
Laboratory of Biochemical Physiology, Frederick Cancer Research and Development Center, National Cancer Institute, Maryland 21702-1201, USA.
Biochemical and biophysical research communications (UNITED STATES) Sep 18 1998, 250 (2) p516-30, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Recent experiments in the Xenopus embryo suggest that proper regulation of **BMP**-4 signaling is critical to the dorsal ventral specification of both mesoderm and ectoderm. Regulation of **BMP**-4 signaling is known to occur extracellularly by direct binding with **chordin**, **noggin**, and **follistatin**, and intracellularly through the antagonistic signal interaction with dorsalizing TGF-beta family member activin. However, tight repressional regulation of **BMP** transcription may also be required to sustain the dorsal and **neural** status of the induced cells. Here we demonstrate that the dominant negative mutant of the **BMP** receptor (DN-BR) or the **BMP**-4 antagonizers, **chordin** and **noggin**, negatively regulate **BMP** -4 transcription in animal cap explants. We

suggest that repression of **BMP**-4 transcription is important in the maintenance of dorsal fate and that continuous input of **BMP**-4 signaling is required to sustain the expression of **BMP** -4 transcription in the maintenance of epidermal/ventral fate. Consistent with this postulation, we found that the promoter region of the isolated **BMP** -4 genomic DNA includes several consensus binding sites for transcriptional regulators functioning under **BMP**-4 signaling such as GATA binding and ventralizing homeobox genes. In a functional assay we found that the GATA binding and ventral homeobox proteins can positively modulate **BMP** -4 promoter activity. We also observed that DN-BR decreases **BMP** -4 promoter activity. This was likely due to a repression of the above-mentioned transcription factors. The significance of these observations to embryonic patterning is discussed.

5/3,AB/37 (Item 37 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09642767 98340018
Xenopus CRMP-2 is an early response gene to **neural** induction.
Kamata T; Daar IO; Subleski M; Copeland T; Kung HF; Xu RH
IRSP, SAIC/Frederick, NCI-FCRDC, Frederick, MD 21702-1201, USA. kamatat@mail.ncifcrf.gov
Brain research. Molecular brain research (NETHERLANDS) Jun 15 1998, 57 (2) p201-10, ISSN 0169-328X Journal Code: MBR
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A **neural** specific protein, CRMP-2 (for Collapsin Response Mediator Protein-2), is considered to mediate collapsin-induced growth cone collapse during **neural** development. We have isolated the Xenopus homologue of the CRMP-2 (XCRMP-2) cDNA and studied the expression of XCRMP-2 mRNA and protein during **neural** induction. Induction of XCRMP-2 mRNA and protein expression, like N-CAM, occurred at the midgastrula stage and increased through early **neural** developmental stages. Whole mount in situ hybridization demonstrated that expression of XCRMP-2 mRNA was localized in **neural** tissues such as the **neural** plate and tube at early stages, while its expression in the brain, spinal cord, and eyes was observed at later stages. Immunostaining of Xenopus embryos with the antibody against CRMP-2 also showed that the protein was specifically expressed in the **neural** tissues at early stages. XCRMP-2 expression was induced by **neural** inducers such as **noggin** and **chordin** which antagonize a **neural** inhibitor, BMP4. A dominant negative **BMP** receptor also induced XCRMP-2 expression, suggesting that transcription of XCRMP-2 gene was negatively regulated by the BMP4 signaling. These results indicate that expression of XCRMP-2 is an early response marking **neural** commitment, and that transcriptional control of XCRMP-2 gene, is one of the targets of BMP4 signaling.

5/3,AB/38 (Item 38 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09586971 98361318
SoxD: an essential mediator of induction of anterior **neural** tissues in Xenopus embryos.
Mizuseki K; Kishi M; Shiota K; Nakanishi S; Sasai Y
Department of Biological Sciences, Kyoto University Faculty of Medicine, Sakyo, Japan.
Neuron (UNITED STATES) Jul 1998, 21 (1) p77-85, ISSN 0896-6273 Journal Code: AN8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Vertebrate neurogenesis is initiated by the organizer factors that

inhibit antineuralizing activities of bone morphogenetic proteins (BMPs) in the ectoderm. Here, we report a candidate mediator of neuralization, SoxD. Expression of SoxD starts at late blastula stages widely in the prospective ectoderm and becomes restricted to the dorsal ectoderm by mid-gastrula stages. SoxD expression is enhanced by the **neural** inducer **Chordin** and is suppressed by BMP4 and its downstream genes. Microinjection of SoxD mRNA causes ectopic formation of **neural** tissues in vivo and induces **neural** and neuronal markers in the isolated animal cap. Injection of a dominant-negative form of SoxD mRNA can block neuralization of ectoderm caused by attenuation of **BMP** signals and can strongly suppress formation of anterior **neural** tissues in vivo. These data show that SoxD functions as an essential mediator of downstream signaling of **neural** induction.

5/3,AB/39 (Item 39 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09561881 98274199
Neural crest induction in Xenopus: evidence for a two-signal model.
LaBonne C; Bronner-Fraser M
Division of Biology, Beckman Institute 139-74, California Institute of Technology, Pasadena, CA 91125, USA. clabonne@caltech.edu
Development (ENGLAND) Jul 1998, 125 (13) p2403-14, ISSN 0950-1991 Journal Code: ECW
Contract/Grant No.: NS36585, NS, NINDS; NS34671, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have investigated the molecular interactions underlying **neural** crest formation in Xenopus. Using **chordin** overexpression to antagonize endogenous **BMP** signaling in whole embryos and explants, we demonstrate that such inhibition alone is insufficient to account for **neural** crest induction in vivo. We find, however, that **chordin** -induced **neural** plate tissue can be induced to adopt **neural** crest fates by members of the FGF and Wnt families, growth factors that have previously been shown to posteriorize induced **neural** tissue. Overexpression of a dominant negative XWnt-8 inhibits the expression of **neural** crest markers, demonstrating the necessity for a Wnt signal during **neural** crest induction in vivo. The requirement for Wnt signaling during **neural** crest induction is shown to be direct, whereas FGF-mediated **neural** crest induction may be mediated by Wnt signals. Overexpression of the zinc finger transcription factor Slug, one of the earliest markers of **neural** crest formation, is insufficient for **neural** crest induction. Slug-expressing ectoderm will generate **neural** crest in the presence of Wnt or FGF-like signals, however, bypassing the need for **BMP** inhibition in this process. A two-step model for **neural** crest induction is proposed.

5/3,AB/40 (Item 40 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09554599 98325381
The Xenopus dorsalizing factor **Gremlin** identifies a novel family of secreted proteins that antagonize **BMP** activities.
Hsu DR; Economides AN; Wang X; Eimon PM; Harland RM
Department of Molecular and Cell Biology, University of California, Berkeley 94720, USA.
Molecular cell (UNITED STATES) Apr 1998, 1 (5) p673-83, ISSN 1097-2765 Journal Code: C5E
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Using a Xenopus expression-cloning screen, we have isolated **Gremlin**

, a novel antagonist of bone morphogenetic protein (**BMP**) signaling that is expressed in the **neural** crest. **Gremlin** belongs to a novel gene family that includes the head-inducing factor Cerberus and the tumor suppressor DAN. We show that all family members are secreted proteins and that they act as **BMP** antagonists in embryonic explants. We also provide support for the model that **Gremlin**, Cerberus, and DAN block **BMP** signaling by binding BMPs, preventing them from interacting with their receptors. In addition, Cerberus alone blocks signaling by Activin- and Nodal-like members of the TGF beta superfamily. Therefore, we propose that **Gremlin** , Cerberus, and DAN control diverse processes in growth and development by selectively antagonizing the activities of different subsets of the TGF beta ligands.

5/3,AB/41 (Item 41 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09547802 98324121
The inductive properties of mesoderm suggest that the neural crest cells are specified by a BMP gradient.
Marchant L; Linker C; Ruiz P; Guerrero N; Mayor R
Laboratory of Developmental Biology, Faculty of Science, University of Chile, Santiago, Chile.
Developmental biology (UNITED STATES) Jun 15 1998, 198 (2) p319-29, ISSN 0012-1606 Journal Code: E7T
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have analyzed the role of mesoderm in the induction of the **neural** crest in Xenopus using expression of **neural** plate (Xsox-2) and **neural** crest (Xslug and ADAM). Conjugation experiments using different kinds of mesoderm together with embryonic dissection experiments suggest that the dorsolateral mesoderm is capable of specifically inducing **neural** crest cells. **Neural** crest markers can be induced in competent ectoderm at varying distances from the inducing mesoderm, with dorsal tissue inducing **neural** crest at a distance while dorsolateral tissue only induces **neural** crest directly in adjacent ectoderm. The results suggest that dorsal mesoderm has a high level of inducer and dorsolateral mesoderm has a lower level, consistent with a inductive gradient. We explored the possible role of **BMP** and **noggin** in the generation of such a hypothetical gradient and found that: (1) progressively higher levels of **BMP** activity are sufficient for the specification of **neural** plate, **neural** crest, and nonneural cells, respectively; (2) progressively higher levels of **noggin** are able to induce **neural** crest at greater distances from the source of inducer; and (3) modification of the levels of **BMP** activity causes induction of the **neural** crest in absence of **neural** plate, suggesting independent induction of these two tissues. We propose a model in which a gradient of **BMP** activity is established in the ectoderm by interaction between **BMP** in the ectoderm and **BMP** inhibitors in the mesoderm. **Neural** crest is induced when a threshold level of **BMP** is attained in the ectoderm. The dorsolateral mesoderm produces either **BMP** inhibitors or a specific **neural** crest inducer, with low **BMP** activity inducing **neural** plate while high **BMP** activity induces epidermis.

5/3,AB/42 (Item 42 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09526853 98252829
Noggin-mediated antagonism of BMP signaling is required for growth and patterning of the neural tube and somite.
McMahon JA; Takada S; Zimmerman LB; Fan CM; Harland RM; McMahon AP

Department of Molecular and Cellular Biology, The Biolabs, Harvard University, [redacted]ridge, Massachusetts 02138, [redacted]A.amcmahon.biosun.harvard.edu
Genes & development (UNITED STATES) May 15 1998, 12 (10) p1438-52, ISSN 0890-9369 Journal Code: FN3
Contract/Grant No.: GM49346, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Embryonic patterning in vertebrates is dependent upon the balance of inductive signals and their specific antagonists. We show that **Noggin**, which encodes a bone morphogenetic protein (**BMP**) antagonist expressed in the node, notochord, and dorsal somite, is required for normal mouse development. Although **Noggin** has been implicated in **neural** induction, examination of null mutants in the mouse indicates that **Noggin** is not essential for this process. However, **Noggin** is required for subsequent growth and patterning of the **neural** tube. Early **BMP**-dependent dorsal cell fates, the roof plate and **neural** crest, form in the absence of **Noggin**. However, there is a progressive loss of early, Sonic hedgehog (Shh)-dependent ventral cell fates despite the normal expression of Shh in the notochord. Further, somite differentiation is deficient in both muscle and sclerotomal precursors. Addition of BMP2 or BMP4 to paraxial mesoderm explants blocks Shh-mediated induction of Pax-1, a sclerotomal marker, whereas addition of **Noggin** is sufficient to induce Pax-1. **Noggin** and Shh induce Pax-1 synergistically. Use of protein kinase A stimulators blocks Shh-mediated induction of Pax-1, but not induction by **Noggin**, suggesting that induction is mediated by different pathways. Together these data demonstrate that inhibition of **BMP** signaling by axially secreted **Noggin** is an important requirement for normal patterning of the vertebrate **neural** tube and somite.

5/3,AB/43 (Item 43 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09433843 98167885
Xenopus Zic-related-1 and Sox-2, two factors induced by **chordin**, have distinct activities in the initiation of **neural** induction.
Mizuseki K; Kishi M; Matsui M; Nakanishi S; Sasai Y
Department of Biological Sciences, Kyoto University Faculty of Medicine, Yoshida, Sakyo, Kyoto 606, Japan.
Development (ENGLAND) Feb 1998, 125 (4) p579-87, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In a differential screen for downstream genes of the **neural** inducers, we identified two extremely early **neural** genes induced by **Chordin** and suppressed by **BMP**-4: Zic-related-1 (Zic-r1), a zinc finger factor related to the Drosophila pair-rule gene odd-paired, and Sox-2, a Sry-related HMG factor. Expression of the two genes is first detected widely in the prospective neuroectoderm at the beginning of gastrulation, following the onset of **Chordin** expression and preceding that of Neurogenin (Xngnr-1). Zic-r1 mRNA injection activates the proneural gene Xngnr-1, and initiates **neural** and neuronal differentiation in isolated animal caps and in vivo. In contrast, Sox-2 alone is not sufficient to cause **neural** differentiation, but can work synergistically with FGF signaling to initiate **neural** induction. Thus, Zic-r1 acts in the pathway bridging the **neural** inducer with the downstream proneural genes, while Sox-2 makes the ectoderm responsive to extracellular signals, demonstrating that the early phase of **neural** induction involves simultaneous activation of multiple functions.

5/3,AB/44 (Item 44 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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09433837 98165404
Chordin regulates primitive streak development and the stability of induced **neural** cells, but is not sufficient for **neural** induction in the chick embryo.
Streit A; Lee KJ; Woo I; Roberts C; Jessell TM; Stern CD
Department of Genetics and Development, College of Physicians and Surgeons of Columbia University, New York, NY 10032, USA.
Development (ENGLAND) Feb 1998, 125 (3) p507-19, ISSN 0950-1991 Journal Code: ECW
Contract/Grant No.: GM53456, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have investigated the role of Bone Morphogenetic Protein 4 (**BMP** -4) and a **BMP** antagonist, **chordin** , in primitive streak formation and **neural** induction in amniote embryos. We show that both **BMP**-4 and **chordin** are expressed before primitive streak formation, and that **BMP**-4 expression is downregulated as the streak starts to form. When **BMP** -4 is misexpressed in the posterior area pellucida, primitive streak formation is inhibited. Misexpression of **BMP** -4 also arrests further development of Hensen's node and axial structures. In contrast, misexpression of **chordin** in the anterior area pellucida generates an ectopic primitive streak that expresses mesoderm and organizer markers. We also provide evidence that **chordin** is not sufficient to induce **neural** tissue in the chick. Misexpression of **chordin** in regions outside the future **neural** plate does not induce the early **neural** markers L5, Sox-3 or Sox-2. Furthermore, neither **BMP**-4 nor **BMP**-7 interfere with **neural** induction when misexpressed in the presumptive **neural** plate before or after primitive streak formation. However, **chordin** can stabilise the expression of early **neural** markers in cells that have already received **neural** inducing signals. These results suggest that the regulation of **BMP** signalling by **chordin** plays a role in primitive streak formation and that **chordin** is not sufficient to induce **neural** tissue.

5/3,AB/45 (Item 45 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09399040 98119828
Regulation of dorsal somitic cell fates: BMPs and **Noggin** control the timing and pattern of myogenic regulator expression.
Reshef R; Maroto M; Lassar AB
Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts 02115, USA.
Genes & development (UNITED STATES) Feb 1 1998, 12 (3) p290-303, ISSN 0890-9369 Journal Code: FN3
Contract/Grant No.: GM54879, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previous work has indicated that signals from the **neural** tube, notochord, and surface ectoderm promote somitic myogenesis. Here, we show that somitic myogenesis is under negative regulation as well; **BMP** signaling serves to inhibit the activation of MyoD and Myf5 in Pax3-expressing cells. Furthermore, we show that the **BMP** antagonist **Noggin** is expressed within the dorsomedial lip of the dermomyotome, where Pax3-expressing cells first initiate the expression of MyoD and Myf5 to give rise to myotomal cells in the medial somite. Consistent with the expression of **Noggin** in dorsomedial dermomyotomal cells that lie adjacent to the dorsal **neural** tube, we have found that coculture of somites with fibroblasts programmed to secrete Wnt1, which is expressed in

dorsal **neural** tube, can induce somitic **Noggin** expression. Ectopic expression of **Noggin** lateral to the somite dramatically expands MyoD expression into the lateral regions of the somite, represses Pax3 expression in this tissue, and induces formation of a lateral myotome. Together, our findings indicate that the timing and location of myogenesis within the somite is controlled by relative levels of **BMP** activity and localized expression of a **BMP** antagonist.

5/3,AB/46 (Item 46 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09383691 98006264

Two closely-related left-right asymmetrically expressed genes, lefty-1 and lefty-2: their distinct expression domains, chromosomal linkage and direct neuralizing activity in Xenopus embryos.

Meno C; Ito Y; Saijoh Y; Matsuda Y; Tashiro K; Kuhara S; Hamada H

Institute for Molecular and Cellular Biology, Osaka University, Suita, Japan.

Genes to cells (ENGLAND) Aug 1997, 2 (8) p513-24, ISSN 1356-9597 Journal Code: CUF

Languages: ENGLISH

Document type: JOURNAL ARTICLE

BACKGROUND: Vertebrates have numerous lateral asymmetries in the position of their organs, but the molecular basis for the determination of left-right (L-R) asymmetries remains largely unknown. TGFbeta-related genes such as lefty and nodal are L-R asymmetrically expressed in developing mouse embryos, and may be involved in L-R determination. RESULTS: We have identified two highly conserved genes, lefty-1 and lefty-2, in the mouse genome. These two genes are tightly linked on mouse chromosome 1. lefty-1 and lefty-2 are both expressed in a L-R asymmetric fashion in mouse embryos. However, the major expression domains of the two genes are different: lefty-1 expression is predominantly confied to the left side of ventral **neural** tube, whereas lefty-2 is strongly expressed in the lateral plate mesoderm on the left side. In embryos homozygous for the iv and inv mutation, which cause situs inversus, the expression sites of both genes are affected, either reversed or bilaterally, indicating that lefty-1 and lefty-2 are downstream of iv and inv. Although Lefty-1 and Lefty-2 prepro-proteins are not readily processed in cultured cells, BMP2-Lefty chimeric proteins can be processed to a secreted form. We have examined the activities of Lefty-1 and Lefty-2 in Xenopus embryos. In animal cap explants, Lefty-1 and Lefty-2 induce **neural** cells in the absence of mesoderm induction. The direct neuralizing activities of Lefty-1 and Lefty-2 thus seem remarkably similar to those of **BMP** antagonists such as **noggin** and **chordin**, suggesting that the action of Lefty-1 and Lefty-2 may be to locally antagonize **BMP** (bone morphogenic protein)-mediated signals in tissues positioned on the left side of the mouse embryos. CONCLUSION: There are two lefty genes in mice (lefty-1 and lefty-2), both of which are expressed in a L-R asymmetric fashion and are downstream of iv and inv. Lefty-1 and Lefty-2 possess direct neuralizing activity in Xenopus embryos, resembling the activities of **BMP** antagonists.

5/3,AB/47 (Item 47 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09324154 98040549

Coordinate actions of BMPs, Wnts, Shh and **noggin** mediate patterning of the dorsal somite.

Marcelle C; Stark MR; Bronner-Fraser M

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Development (ENGLAND) Oct 1997, 124 (20) p3955-63, ISSN 0950-1991 Journal Code: D
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Shortly after their formation, somites of vertebrate embryos differentiate along the dorsoventral axis into sclerotome, myotome and dermomyotome. The dermomyotome is then patterned along its mediolateral axis into medial, central and lateral compartments, which contain progenitors of epaxial muscle, dermis and hypaxial muscle, respectively. Here, we used Wnt-11 as a molecular marker for the medial compartment of dermomyotome (the 'medial lip') to demonstrate that **BMP** in the dorsal **neural** tube indirectly induces formation of the medial lip by up-regulating Wnt-1 and Wnt-3a (but not Wnt-4) expression in the **neural** tube. **Noggin** in the dorsal somite may inhibit the direct action of **BMP** on this tissue. Wnt-11 induction is antagonized by Sonic Hedgehog, secreted by the notochord and the floor plate. Together, our results show that the coordinated actions of the dorsal **neural** tube (via **BMP** and Wnts), the ventral **neural** tube/notochord (via Shh) and the somite itself (via **noggin**) mediates patterning of the dorsal compartment of the somite.

5/3,AB/48 (Item 48 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09294512 97474317

A role for the roof plate and its resident TGFbeta-related proteins in neuronal patterning in the dorsal spinal cord.

Liem KF Jr; Tremml G; Jessell TM
Department of Biochemistry and Molecular Biophysics, Center for Neurobiology and Behavior, Columbia University, New York, New York 10032, USA.

Cell (UNITED STATES) Oct 3 1997, 91 (1) p127-38, ISSN 0092-8674 Journal Code: CQ4
Contract/Grant No.: 5T32GM07367, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Distinct neuronal cell types are generated at characteristic times and positions in the dorsal horn of the spinal cord. We provide evidence that the identity and pattern of generation of dorsal neurons depend initially on **BMP** -mediated signals that derive from the epidermal ectoderm and induce dorsal midline cells of the roof plate. Roof plate cells provide a secondary source of TGFbeta-related signals that are required for the generation of distinct classes of dorsal interneurons. These inductive interactions involve both qualitative and quantitative differences in signaling by TGFbeta-related factors and temporal changes in the response of **neural** progenitor cells.

5/3,AB/49 (Item 49 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09250000 97426538

Studies on the role of fibroblast growth factor signaling in neurogenesis using conjugated/aged animal caps and dorsal ectoderm-grafted embryos.

Xu RH; Kim J; Taira M; Sredni D; Kung H
Intramural Research Support Program, Science Applications International Corporation-Frederick, Frederick, Maryland 21702-1201, USA.

Journal of neuroscience (UNITED STATES) Sep 15 1997, 17 (18) p6892-8, ISSN 0270-6474 Journal Code: JDF
Languages: ENGLISH
Document type: JOURNAL ARTICLE

Basic fibroblast growth factor (bFGF) has been shown to induce

neural fate in dissociated animal cap (AC) cells or in AC explants cultured in low calcium and magnesium concentrations. However, long-term disclosure of the cap may cause diffusion of the secreted molecule bone morphogenetic protein 4 (**BMP**-4), a **neural** inhibitor present in the AC. This may contribute to the subsequent neurogenesis induced by bFGF. Here we used conjugated and aged blastula AC to avoid diffusion of endogenous molecules from the AC. Unlike **noggin**, bFGF failed to induce **neural** tissue in this system. However, it enhanced neuralization elicited by a dominant negative **BMP** receptor (DN-BR) that inhibits the **BMP**-4 signaling. Posterior **neural** markers were turned on by bFGF in AC expressing DN-BR or **chordin**. Blocking the endogenous FGF signal with a dominant negative FGF receptor (XFD) mainly inhibited development of posterior **neural** tissue in neuralized ACs. These in vitro studies were confirmed in vivo in embryos grafted with XFD-expressing ACs in the place of neuroectoderm. Expression of some regional **neural** markers was inhibited, although markers for muscle and posterior notochord were still detectable in the grafted embryos, suggesting that XFD specifically affected neurogenesis but not the dorsal mesoderm. The use of these in vitro and in vivo model systems provides new evidence that FGF, although unable to initiate neurogenesis on its own, is required for **neural** induction as well as for posteriorization.

5/3,AB/50 (Item 50 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09220236 97417585
Concentration-dependent patterning of the Xenopus ectoderm by BMP4 and its signal transducer Smad1.
Wilson PA; Lagna G; Suzuki A; Hemmati-Brivanlou A
Department of Molecular Embryology, The Rockefeller University, New York, NY 10021, USA.
Development (ENGLAND) Aug 1997, 124 (16) p3177-84, ISSN 0950-1991 Journal Code: ECW
Contract/Grant No.: 1 R01 HD 32105-01, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Morphogens are thought to establish pattern in early embryos by specifying several cell fates along a gradient of concentration; a well-studied example is the Drosophila protein decapentaplegic (DPP) acting in the wing disc. Recent work has established that bone morphogenetic protein 4 (BMP4), the vertebrate homologue of DPP, controls the fundamental choice between **neural** and epidermal fates in the vertebrate ectoderm, under the control of antagonists secreted by the organizer region of the mesoderm. We now show that BMP4 can act as a morphogen, evoking distinct responses in Xenopus ectodermal cells at high and low concentrations, in a pattern consistent with the positions of the corresponding cell types in the embryo. Moreover, this complex cellular response to extracellular BMP4 concentration does not require subsequent cell-cell communication and is thus direct, as required of a classical morphogen. We also show that the same series of cell types--epidermis, cement gland and **neural** tissue--can be produced by progressively inhibiting endogenous **BMP** signaling with specific antagonists, including the organizer factor **noggin** . Finally, expression of increasing doses of the signal transduction molecule Smad1 accurately reproduces the response to BMP4 protein. Since Smads have been shown to act in the nucleus, this finding implies a direct translation of extracellular morphogen concentration into transcription factor activity. We propose that a graded distribution of **BMP** activity controls the specification of several cell types in the gastrula ectoderm and that this extracellular gradient acts by establishing an intracellular and then nuclear gradient of Smad activity.

5/3,AB/51 (Item 51 from file: 155)

DIALOG(R)File 155:MEDLINE(R)
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09218108 97296446
A graded response to **BMP**-4 spatially coordinates patterning of the mesoderm and ectoderm in the zebrafish.
Neave B; Holder N; Patient R
Division of Biomedical Sciences, King's College, London, UK.
Mechanisms of development (IRELAND) Mar 1997, 62 (2) p183-95, ISSN 0925-4773 Journal Code: AXF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The effects of signal perturbation on expression domains of molecular markers for the mesoderm and ectoderm have been analysed across the dorso-ventral axis in zebrafish embryos. Injection of RNA encoding bone morphogenetic protein-4 (**BMP**-4) ventralised the embryo, expanding the intermediate mesoderm and non-**neural** ectoderm at the expense of the dorso-anterior mesoderm and **neural** plate. A dose-dependent response was observed both morphologically and in expression of gta3, MyoD and pax2. Conversely, increases in dorso-anterior mesoderm and neurectoderm were generated by injection of RNA encoding either a dominant-negative **BMP** receptor (delta BMPR) or **noggin**, as demonstrated by goosecoid and pax2 expression. Ventral **BMP**-4 expression was also inhibited. Thus, patterning of both the mesoderm and the ectoderm during gastrulation appears to depend, directly or indirectly, on the level of **BMP** activity. Consistent with their locations prior to formation of the **neural** tube, elevated **BMP** -4 increased the number of dorsal spinal cord neurons whilst sonic hedgehog and islet1 expression in the ventral spinal cord were reduced. However, the ectopic neurons were not positioned more ventrally, implicating a prepattern in the dorsal **neural** tube that is independent of the ventral central nervous system.

5/3,AB/52 (Item 52 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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09179651 97321545
The dorsalizing and **neural** inducing gene **follistatin** is an antagonist of **BMP**-4.
Fainsod A; Deissler K; Yelin R; Marom K; Epstein M; Pillemer G; Steinbeisser H; Blum M
Department of Cellular Biochemistry, Hebrew University-Hadassah Medical School, Jerusalem, Israel. fainsod@gene.tnd.huji.ac.il
Mechanisms of development (IRELAND) Apr 1997, 63 (1) p39-50, ISSN 0925-4773 Journal Code: AXF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Specific signaling molecules play a pivotal role in the induction and specification of tissues during early vertebrate embryogenesis. **BMP**-4 specifies ventral mesoderm differentiation and inhibits **neural** induction in Xenopus, whereas three molecules secreted from the organizer, **noggin**, **follistatin** and **chordin** dorsalize mesoderm and promote **neural** induction. Here we report that **follistatin** antagonizes the activities of **BMP** -4 in frog embryos and mouse teratocarcinoma cells. In Xenopus embryos **follistatin** blocks the ventralizing effect of **BMP**-4. In mouse P19 cells **follistatin** promotes **neural** differentiation. **BMP**-4 antagonizes the action of **follistatin** and prevents **neural** differentiation. In addition we show that the **follistatin** and **BMP**-4 proteins can interact directly in vitro. These data provide evidence that **follistatin** might play a role in modulating **BMP**-4 activity in vivo.

5/3,AB/53 (Item 53 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09179587 97327682
Chick **noggin** is expressed in the organizer and **neural** plate during axial development, but offers no evidence of involvement in primary axis formation.
Connolly DJ; Patel K; Cooke J
Division of Developmental Neurobiology, National Institute for Medical Research, London, United Kingdom.
International journal of developmental biology (SPAIN) Apr 1997, 41 (2) p389-96, ISSN 0214-6282 Journal Code: AV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have cloned and examined the early developmental expression of the chick homolog of **noggin**, a gene originally isolated in Xenopus that can dorsalize gastrular mesoderm and induce anterior **neural** tissue from gastrular ectoderm when expressed experimentally. Chick **noggin** is expressed at relatively low levels, but at sites equivalent to those seen in amphibian development, namely Hensen's node and the endo- and mesodermal head process. There is also diffuse expression in the early CNS, centered on the ventral midline, and later hindbrain-associated expression. Since the earlier of these expression sites are consistent with endogenous organizer functions suggested by the properties of the protein in Xenopus experiments, we have used recombinant mammalian **Noggin** protein secreted by CHO cells in tests for developmental disturbance on the early gastrula-staged chick blastoderm. Comparable tests sensitively detect effects, on chick, of various other secreted proteins that simulate or replicate early developmental signals in Xenopus. We have been unable to observe such effects with a range of **Noggin** concentrations including those that dramatically dorsalize Xenopus ventral marginal zones. To illustrate effects observed in such tests with secreted proteins active on early stages, we show results with the known Xenopus ventralizer Bone Morphogenetic Protein 4 (**BMP**-4).

5/3,AB/54 (Item 54 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09166167 97342676
Mechanisms of dorsal-ventral patterning in **noggin**-induced **neural** tissue.
Knecht AK; Harland RM
Department of Molecular and Cell Biology, University of California at Berkeley, 94720-3204, USA.
Development (ENGLAND) Jun 1997, 124 (12) p2477-88, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have investigated mechanisms of dorsal-ventral patterning of **neural** tissue, using Xenopus ectoderm neuralized by **noggin** protein. This tissue appears to be patterned dorsoventrally; cp1-1, a gene expressed in the dorsal brain, and etr-1, a gene largely excluded from the dorsal brain, are expressed in separate territories in **noggin**-treated explants (Knecht, A. K., Good, P. J., Dawid, I. B. and Harland, R. M. (1995) Development 121, 1927-1936). Here we show further evidence that this pattern represents a partial dorsal-ventral organization. Additionally, we test two mechanisms that could account for this pattern: a dose-dependent response to a gradient of **noggin** protein within the explant, and regulative cell-cell interactions. We show that **noggin** exhibits concentration-dependent effects, inducing cp1-1 at low doses but repressing it at high doses. Since **noggin** acts by antagonizing Bone Morphogenetic Protein (**BMP**) signaling, this result suggests that BMPs

also may act in a dose-dependent manner in vivo. However, in the absence of a **noggin** gradient, regulative cell-cell interactions can also pattern the tissue. Such regulation is facilitated by increased motility of **noggin**-treated cells. Finally, the response of cells to both of these patterning mechanisms is ultimately controlled by a third process, the changing competence of the responding tissue.

5/3,AB/55 (Item 55 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09143560 97304610

Target tissue influence on somatostatin expression in the avian ciliary ganglion.

Coulombe JN; Kos K

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Annals of the New York Academy of Sciences (UNITED STATES) Apr 24 1997, 814 p209-25, ISSN 0077-8923 Journal Code: 5NM

Languages: ENGLISH

Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL

Activin as a neurodifferentiation factor. Our studies of neurotransmitter expression have focused on the expression of neuropeptide transmitters in the avian ciliary ganglion (CG) and have examined the influence of choroidal vascular smooth muscle cells in regulating the differential expression of somatostatin in the CG. In these activities we have identified activin A as a potential target-derived neurodifferentiation factor that can stimulate somatostatin expression in cultured CG neurons. In cultured CG neurons, activin can stimulate the expression of somatostatin in choroid neurons, the pattern of neurotransmitter expression found in vivo, and in the ciliary neurons that would normally not express somatostatin. In vivo, mRNA transcripts of the cActR-IIA appear to be expressed by both choroid and ciliary CG neurons. This suggests that activin might serve as an instructive factor in controlling neuropeptide phenotype. For activin to serve as an instructive factor requires that activin be produced by choroid smooth-muscle target cells. Indeed, activin mRNA and activin-like immunoreactivity are found in choroid cells, in vitro. However, the lack of somatostatin expression by ciliary neurons suggests that activin is not produced by their targets, the iris and ciliary body. This simple view is countered by the observation that activin A mRNA is also present in the iris and activin-like immunoreactivity is detectable in the iris and ciliary body. Instead, the production of the specific activin inhibitor **follistatin** in the iris and ciliary body is likely to limit the availability of activin to only those neurites innervating the choroid layer, thus accounting for the differential expression of somatostatin in only the choroid CG neurons. This somewhat more complicated arrangement is similar to the mechanism thought to be employed for primary induction during frog embryogenesis. The observations reviewed here are all consistent with the hypothesized role for activin as a molecule whose availability to neurites in the target regulates neurotransmitter expression. Additional in vivo perturbation experiments are needed to further examine this hypothesis; nevertheless, activin appears as a strong candidate for a target-derived neurotransmitter differentiation factor. Activin's potential roles in differentiation: A wide variety of biological effects have been ascribed to activin. Initially identified and purified as a gonadal hormone stimulating the production and release of FSH from the pituitary, activin is also implicated in the stimulation of erythroid differentiation, as a modulator of follicular granulosa cell differentiation, as a mesodermalizing factor in both amphibian and avian early development, and as a component in establishing left-right axial patterning in the chicken embryo. Activin has also been found to be a survival factor for several neuronal cell lines and for rat embryonic **neural** retina cells in culture. However, activin is not a survival factor for chicken CG neurons in culture. Our observation that

activin may play a function in target-derived control of neuropeptide expression add[redacted]et another aspect to the list[redacted] its potential biological functions. In addition, activin shares regi[redacted]s of amino acid sequence identity with members of the TGF-beta superfamily, which includes the TGF-betas, Mullerian inhibitory substance, Drosophila decapentaplegic gene product, dorsalin, bone morphogenetic proteins, inhibin, and glial-derived neurotrophic factor. Interestingly, these are all factors that have effects upon cellular differentiation. Effects of activin on other neurons. Activin A--as well as two other TGF-beta superfamily members, **BMP**-2 and **BMP** -6--has been shown to induce expression of mRNAs for several neuropeptides in cultured rat sympathetic neurons. In addition, activin A induces ChAT mRNA in cultured sympathetic neurons. (ABSTRACT TRUNCATED)

5/3,AB/56 (Item 56 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09090145 97228548
Ectodermal patterning in vertebrate embryos.
Sasai Y; De Robertis EM
Howard Hughes Medical Institute, University of California, Los Angeles 90095-1737, USA.
Developmental biology (UNITED STATES) Feb 1 1997, 182 (1) p5-20, ISSN 0012-1606 Journal Code: E7T
Contract/Grant No.: HD 21502-11, HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Recent molecular insights on how the ectodermal layer is patterned in vertebrates are reviewed. Studies on the induction of the central nervous system (CNS) by Spemann's Organizer led to the isolation of **noggin** and **chordin** . These secretory proteins function by binding to, and inhibiting, ventral BMPs, in particular **BMP**-4. **Neural** induction can be considered as the dorsalization of ectoderm, in which low levels of **BMP**-signaling result in CNS formation. At high levels of **BMP** signaling the ectoderm adopts a ventral fate and skin is formed. In Xenopus the forming **neural** plate already has extensive dorsal-ventral (D-V) patterning, and **neural** induction and D-V patterning may share common molecular mechanisms. At later stages sonic hedgehog (shh) plays a principal role in D-V patterning, particularly in the **neural** tube of the amniote embryo. A great many transcription factor markers are available and mouse knockouts provide evidence of their involvement in the regional specification of the **neural** tube. Recent evidence indicating that differentiation of posterior CNS is promoted by FGF, Wnt-3a, and retinoic acid is reviewed from the point of view of the classical experiments of Nieuwkoop that defined an activation and a transformation step during **neural** induction.

5/3,AB/57 (Item 57 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

09060731 97127400
Differential regulation of neurogenesis by the two Xenopus GATA-1 genes.
Xu RH; Kim J; Taira M; Lin JJ; Zhang CH; Sredni D; Evans T; Kung HF
Laboratory of Biochemical Physiology, National Cancer Institute-Frederick Cancer Research and Development Center, Maryland 21702-1201, USA.
Molecular and cellular biology (UNITED STATES) Jan 1997, 17 (1) p436-43, ISSN 0270-7306 Journal Code: NGY
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Previously, we have shown that the ventralizing factor bone morphogenetic protein 4 (**BMP** -4) can inhibit Xenopus neurogenesis. The erythroid transcription factor GATA-1 functions downstream of the **BMP** -4

signaling pathway and mediates **BMP**-4-induced erythropoiesis. We have found that similar to **BMP** -4, GATA-1b inhibits neuralization of Xenopus animal cap (AC) cells. The **neural** inhibition is not seen with GATA-1a, although both GATA-1a and GATA-1b RNAs are translated at the same efficiency and induce globin expression equally in AC cells. GATA-1b RNA injection into AC cells neither induces expression of Xbra (a general mesoderm marker) nor affects expression of XK81 (epidermal keratin) or **BMP** -4 and Xvent-1 (two ventral markers). These data suggest that GATA-1b retains the epidermal fate of the AC. Intact GATA-1b protein is required for both inhibition of neurogenesis and induction of globin expression. Our findings indicate that GATA-1b can function in ectoderm to specifically regulate **neural** inducing mechanisms, apparently related to the expression of **chordin** , a neuralizing gene. Furthermore, tadpole stage embryos injected with GATA-1b are devoid of all dorsoanterior structures including **neural** tissue. This report provides evidence that the two transcription factors, derived from a recent genome duplication, share a common biological activity (stimulation of erythropoiesis) while also exhibiting a distinct function (inhibition of neurogenesis).

5/3,AB/58 (Item 58 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08936563 97164716

The Drosophila decapentaplegic and short gastrulation genes function antagonistically during adult wing vein development.

Yu K; Sturtevant MA; Biehs B; Francois V; Padgett RW; Blackman RK; Bier E
Department of Biology and Center for Molecular Genetics, University of California, San Diego, La Jolla 92093, USA.

Development (ENGLAND) Dec 1996, 122 (12) p4033-44, ISSN 0950-1991
Journal Code: ECW
Contract/Grant No.: RO1-NS29870-01, NS, NINDS
Languages: ENGLISH
Document type: JOURNAL ARTICLE

TGF-beta-related signaling pathways play diverse roles during vertebrate and invertebrate development. A common mechanism for regulating the activity of TGF-beta family members is inhibition by extracellular antagonists. Recently, the Drosophila short gastrulation (sog) gene was shown to encode a predicted diffusible factor which antagonizes signaling mediated by the TGF-beta-like Decapentaplegic (Dpp) pathway in the early blastoderm embryo. sog and dpp, which are among the earliest zygotic genes to be activated, are expressed in complementary dorsal-ventral domains. The opposing actions of sog and dpp in the early embryo have been highly conserved during evolution as their vertebrate counterparts, **chordin** and **BMP**-4, function homologously to define **neural** versus non-**neural** ectoderm in Xenopus. Here we exploit the genetically sensitive adult wing vein pattern to investigate the generality of the antagonistic relationship between sog and dpp. We show that dpp is expressed in vein primordia during pupal wing development and functions to promote vein formation. In contrast, sog is expressed in complementary intervein cells and suppresses vein formation. sog and dpp function during the same phenocritical periods (i.e. 16-28 hours after pupariation) to influence the vein versus intervein cell fate choice. The conflicting activities of dpp and sog are also revealed by antagonistic dosage-sensitive interactions between these two genes during vein development. Analysis of vein and intervein marker expression in dpp and sog mutant wings suggests that dpp promotes vein fates indirectly by activating the vein gene rhomboid (rho), and that sog functions by blocking an autoactivating Dpp feedback loop. These data support the view that Sog is a dedicated Dpp antagonist.

5/3,AB/59 (Item 59 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08869348 97042346

Endoderm induction by the organizer-secreted factors **chordin** and **noggin** in Xenopus animal caps.

Sasai Y; Lu B; Piccolo S; De Robertis EM

Department of Biological Chemistry, University of California, Los Angeles 90095-1737, USA.

EMBO journal (ENGLAND) Sep 2 1996, 15 (17) p4547-55, ISSN 0261-4189 Journal Code: EMB

Contract/Grant No.: HD21502-11, HD, NICHD

Languages: ENGLISH

Document type: JOURNAL ARTICLE

Spemann's organizer has potent **neural** inducing and mesoderm dorsalizing activities in the Xenopus gastrula. A third activity, the organizer's ability to induce a secondary gut, has been difficult to analyze experimentally due to the lack of early gene markers. Here we introduce endodermin, a pan-endodermal gene marker, and use it to demonstrate that **chordin** (Chd), a protein secreted by the organizer region, is able to induce endodermal differentiation in Xenopus. The ability of chd, as well as that of **noggin**, to induce endoderm in animal cap explants is repressed by the ventralizing factor **BMP**-4. When FGF signaling is blocked by a dominant-negative FGF receptor in chd-injected animal caps, **neural** induction is inhibited and most of the explant is induced to become endoderm. The results suggest that proteins secreted by the organizer, acting together with known peptide growth factors, regulate differentiation of the endodermal germ layer.

5/3,AB/60 (Item 60 from file: 155)

DIALOG(R)File 155:MEDLINE(R)

08840156 97078768

The Drosophila short gastrulation gene prevents Dpp from autoactivating and suppressing neurogenesis in the neuroectoderm.

Biehs B; Francois V; Bier E

Department of Biology, University of California, San Diego, La Jolla 92093, USA.

Genes & development (UNITED STATES) Nov 15 1996, 10 (22) p2922-34, ISSN 0890-9369 Journal Code: FN3

Contract/Grant No.: RO1-NS29870, NS, NINDS

Languages: ENGLISH

Document type: JOURNAL ARTICLE

The short gastrulation (sog) gene is expressed in broad lateral stripes comprising the neuroectoderm of the Drosophila blastoderm embryo. sog encodes a predicted secreted protein that functions nonautonomously to antagonize the activity of the TGF-beta-like Decapentaplegic (Dpp) signaling pathway in the dorsal region of the embryo. Recently, it has been shown that sog and dpp are functionally equivalent to their respective Xenopus homologs **chordin** and **BMP**-4. In this report we provide the first direct evidence that sog plays a local role in the lateral region of the blastoderm embryo to oppose Dpp activity in the neuroectoderm. In the dorsal region, Dpp signaling both suppresses neurogenesis and maintains expression of genes that promote dorsal cell fates (dorsalization). We show that Dpp also can perform both of these functions in the neuroectoderm. In wild-type embryos, the ability of Dpp to induce expression of dorsal markers including itself (autoactivation) in the neuroectoderm is blocked by sog. We propose that Sog protects the neuroectoderm from an invasive positive feedback loop created by Dpp diffusion and autoactivation. We show that the two functions of Dpp signaling, **neural** suppression and dorsalization, are triggered by distinct thresholds of Dpp activity. Epistasis experiments reveal that all observed sog activity can be accounted for by Sog functioning as a dedicated Dpp antagonist. Finally, we provide evidence that Sog functions as a diffusible morphogen in the

blastoderm embryo. These data strongly support the view that the primary phylogenetically conserved function of the Drosophila sog and dpp genes and the homologous Xenopus **chordin** and **BMP**-4 genes is to subdivide the primitive embryonic ectoderm into **neural** versus non-**neural** domains.

5/3,AB/61 (Item 61 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08837612 97053805
The homeobox gene Siamois is a target of the Wnt dorsalisation pathway and triggers organiser activity in the absence of mesoderm.
Carnac G; Kodjabachian L; Gurdon JB; Lemaire P
Wellcome/CRC Institute, Cambridge, United Kingdom.
Development (ENGLAND) Oct 1996, 122 (10) p3055-65, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Siamois, a Xenopus zygotic homeobox gene with strong dorsalising activity, is expressed in the dorsal-vegetal organiser known as the Nieuwkoop centre. We show that, in contrast to Spemann organiser genes such as goosecoid, **chordin** and **noggin**, Siamois gene expression is not induced following overexpression of mesoderm inducers in ectodermal (animal cap) cells. However, Siamois is induced by overexpressing a dorsalising Wnt molecule. Furthermore, like Wnt, Siamois can dorsalise ventral mesoderm and cooperate with Xbrachyury to generate dorsal mesoderm. These results suggest that Siamois is a mediator of the Wnt-signalling pathway and that the synergy between the Wnt and mesoderm induction pathways occurs downstream of the early target genes of these two pathways. Overexpression of Siamois in animal cap cells reveals that this gene can act in a non vegetal or mesodermal context. We show the following. (1) Animal cap cells overexpressing Siamois secrete a factor able to dorsalise ventral gastrula mesoderm in tissue combination experiments. (2) The Spemann organiser-specific genes goosecoid, Xnr-3 and **chordin**, but not Xlim.1, are activated in these caps while the ventralising gene **Bmp** -4 is repressed. However, the dorsalising activity of Siamois-expressing animal caps is significantly different from that of **noggin**- or **chordin** -expressing animal caps, suggesting the existence of other dorsalising signals in the embryo. (3) Ectodermal cells overexpressing Siamois secrete a neuralising signal and can differentiate into cement gland and, to a lesser extent, into **neural** tissue. Hence, in the absence of mesoderm induction, overexpression of Siamois is sufficient to confer organiser properties on embryonic cells.

5/3,AB/62 (Item 62 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08828259 97003224
A sticky problem: the Xenopus cement gland as a paradigm for anteroposterior patterning.
Sive H; Bradley L
Whitehead Institute for Biomedical Research, Cambridge, Massachusetts 02142, USA.
Developmental dynamics (UNITED STATES) Mar 1996, 205 (3) p265-80, ISSN 1058-8388 Journal Code: A9U
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The cement gland is a mucus-secreting organ found at the extreme anterior of frog embryos. It attaches the embryo to a solid support before swimming and feeding begin, and also serves a related sensory function that stops the embryo from moving once it is attached. Cement gland is an extremely

useful anterior marker, whose study continues to yield fundamental information concerning vertebrate axial patterning. Cement gland arises from the outer layer of the embryonic ectoderm and, in Xenopus, forms a cone of columnar epithelium. It is the first ectodermal organ to differentiate, beginning to do so by late gastrula. A battery of genes expressed in the developing and mature cement gland serve as useful markers. Cement gland development can be influenced by both stimulatory and inhibitory cell interactions. Stimulatory signals arise from the anterior **neural** plate, head endoderm, and the dorsal mesoderm. Inhibitory signals are present in the posterior dorsal mesoderm and in ventral ectoderm and mesoderm. Further, signalling between the ectodermal layers may restrict cement gland differentiation to the outer ectodermal cells. Several secreted molecules are able to induce or repress cement gland formation: these include **noggin**, **follistatin**, hedgehog, **chordin** , retinoic acid, embryonic fibroblast growth factor (eFGF), Bone Morphogenetic Protein-4 (**BMP**-4), and Xwnt-8. Several of these factors alter expression of the homeodomain gene Xotx2, which may be a transcriptional activator of cement gland differentiation genes. The significance of the cell interactions and factors described in positioning cement gland at the front of the embryo is explored.

5/3,AB/63 (Item 63 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08825855 96337487
Factors responsible for the establishment of the body plan in the amphibian embryo.
Grunz H
Universitat GH Essen, FB 9 (Biologie), Department of Zoophysiology, Germany. h.grunz@uni-essen.de
International journal of developmental biology (SPAIN) Feb 1996, 40 (1) p279-89, ISSN 0214-6282 Journal Code: AV3
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
A central topic of embryology is the establishment of the body plan during embryogenesis. Starting with maternal factors distributed in the early cleavage stages in distinct patterns and gradients cell-to-cell interactions including early embryonic induction result in the formation of mesoderm and the organizer area. While many facts are known about the role of growth factors like activin (closely related to the vegetalizing factor), processed Vg1, BMPs and FGF for mesoderm formation, the establishment of the central nervous system is not yet well understood. However, there is growing evidence that **neural** induction is a multistep process at the level of the dorsal mesoderm (organizer) and the reacting neuroectoderm. Therefore the existence of only one neuralizing factor is unlikely. We report about data that **follistatin** protein is not a direct **neural** inducer. Furthermore our comparative studies of Xenopus and Triturus exogastrulae indicate that planar signals are unlikely in the Triturus embryo (urodeles) during the early steps of **neural** induction. Vertical signals emanating from the chordamesoderm are essential for the terminal neuralization and regionalization of the central nervous system during gastrulation for both Xenopus and Triturus. The putative role of neuralizing factors and **BMP** /activin-like molecules for the stabilization or shift of neuroectoderm into different pathways of differentiation (epidermis or **neural** default state) is discussed.

5/3,AB/64 (Item 64 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08793941 96361357
The Spemann organizer signal **noggin** binds and inactivates bone

morphogenetic protein 4.
Zimmerman LB; [redacted] Jesus-Escobar JM; Harland RM [redacted]
Department of Molecular and Cell Biology, Division of Biochemistry and Molecular Biology, University of California, Berkeley 94720, USA.
Cell (UNITED STATES) Aug 23 1996, 86 (4) p599-606, ISSN 0092-8674 Journal Code: CQ4
Contract/Grant No.: GM 15782, GM, NIGMS; GM 49346, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Signals released by the Spemann organizer of the amphibian gastrula can directly induce **neural** tissue from ectoderm and can dorsalize ventral mesoderm to form muscle. The secreted polypeptide **noggin** mimics these activities and is expressed at the appropriate time and place to participate in the organizer signal. **Neural** induction and mesoderm dorsalization are antagonized by bone morphogenetic proteins (BMPs), which induce epidermis and ventral mesoderm instead. Here we report that **noggin** protein binds BMP4 with high affinity and can abolish BMP4 activity by blocking binding to cognate cell-surface receptors. These data suggest that **noggin** secreted by the organizer patterns the embryo by interrupting **BMP** signaling.

5/3,AB/65 (Item 65 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08793112 96312918
Xom: a Xenopus homeobox gene that mediates the early effects of **BMP** -4.
Ladher R; Mohun TJ; Smith JC; Snape AM
Division of Developmental Biology, National Institute for Medical Research, London, UK.
Development (ENGLAND) Aug 1996, 122 (8) p2385-94, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Bone morphogenetic protein-4 (**BMP** -4) is thought to play an important role in early Xenopus development by acting as a "ventralizing factor' and as an epidermal determinant: local inhibition of **BMP**-4 function in whole embryos causes the formation of an additional dorsal axis, and inhibition of **BMP**-4 function in isolated ectodermal cells causes the formation of **neural** tissue. In this paper we describe a homeobox-containing gene whose expression pattern is similar to that of **BMP**-4, whose expression requires **BMP**-4 signalling and which, when over-expressed, causes a phenotype similar to that caused by over-expression of **BMP** -4. We suggest that this gene, which we call Xom, acts downstream of **BMP**-4 to mediate its effects.

5/3,AB/66 (Item 66 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08791308 96232286
Regulation of dorsal-ventral patterning: the ventralizing effects of the novel Xenopus homeobox gene Vox.
Schmidt JE; von Dassow G; Kimelman D
Department of Biochemistry, University of Washington, Seattle, 98195-7350, USA.
Development (ENGLAND) Jun 1996, 122 (6) p1711-21, ISSN 0950-1991 Journal Code: ECW
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The formation of the dorsal-ventral axis in Xenopus laevis is elicited by a signaling cascade on the dorsal side of the embryo initiated by cortical

rotation. These early developmental events impart an initial axial polarity to the embryo [redacted] the time gastrulation occurs, [redacted]e embryo has established opposing dorsal and ventral regulatory regions. Through a dynamic process, the embryo acquires a definitive pattern that reflects the distribution of future cell fates. Here we present a novel homeobox gene, Vox, whose expression reflects this dynamic process. Vox is first expressed throughout the embryo and subsequently eliminated from the notochord and **neural** plate. Ectopic expression of Vox demonstrates that the normal function of this gene may be to suppress dorsal genes such as Xnot and **chordin**, and induce ventral and paraxial genes such as **Bmp**-4 and MyoD. Ectopic expression of **BMP**-4 ventralizes embryos and positively regulates the expression of Vox, suggesting that these genes are components of a reciprocal regulatory network.

5/3,AB/67 (Item 67 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08553279 96189487
Mesoderm-inducing factors and mesodermal patterning.
Smith JC
Division of Developmental Biology, National Institute for Medical Research, London, UK. j-im@nimr.mrc.ac.uk
Current opinion in cell biology (UNITED STATES) Dec 1995, 7 (6) p856-61, ISSN 0955-0674 Journal Code: AOE
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Identification of the signalling molecules involved in mesoderm formation in amphibian embryos still presents problems. None of the original candidates, such as activin, have been definitively ruled out, and new factors, such as the nodal-related genes, have come on to the scene. Of the original candidates, activin has been definitively shown to act as a morphogen, whereas bone morphogenetic protein (**BMP**)-4 has emerged as a ventral inducer and an inhibitor of **neural** differentiation. The effects of **BMP**-4 are antagonized by **chordin**, a molecule related to the product of the Drosophila gene short gastrulation.

5/3,AB/68 (Item 68 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08550415 96077118
Regulation of **neural** induction by the Chd and **Bmp** -4 antagonistic patterning signals in Xenopus.
Sasal Y; Lu B; Steinbelsser H; De Robertis EM
Nature (ENGLAND) Nov 23 1995, 378 (6555) p419, ISSN 0028-0836 Journal Code: NSC
Languages: ENGLISH
Document type: PUBLISHED ERRATUM

5/3,AB/69 (Item 69 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08545681 95356812
Induction of epidermis and inhibition of **neural** fate by **Bmp** -4.
Wilson PA; Hemmati-Brivanlou A
Rockefeller University, New York, New York 10021-6322, USA.
Nature (ENGLAND) Jul 27 1995, 376 (6538) p331-3, ISSN 0028-0836 Journal Code: NSC
Languages: ENGLISH

Document type: JOURNAL ARTICLE
During gastrulation in vertebrates, ectoderm cells choose between two fates, **neural** and epidermal. The nervous system forms in response to signals from the Spemann organizer; ectoderm that does not receive these signals becomes epidermis. Unexpectedly, however, in Xenopus, **neural** tissue also forms when cell-cell communication within the ectoderm is disrupted by cell dissociation or by antagonists of the growth factor activin. These observations suggest that epidermal specification depends on local signalling, by activin or a close relative, and that **neural** tissue forms when this communication is blocked. Here we report that bone morphogenesis protein 4 (**Bmp** -4), a relative of activin that is expressed in the embryo at the time of ectodermal fate determination, is a potent epidermal inducer and **neural** inhibitor, the first reported in any vertebrate. Activin can inhibit neuralization by inducing mesoderm, but does not induce epidermis. Moreover, the dominant-negative activin receptor, which stimulates neuralization when expressed in the embryo, blocks **Bmp** -4 in our assay. Our findings demonstrate that epidermal fate can be induced, and thus provide further evidence that **neural** specification is under inhibitory control in vertebrates.

5/3,AB/70 (Item 70 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08544863 95336445
A dominant negative bone morphogenetic protein 4 receptor causes neuralization in Xenopus ectoderm.
Xu RH; Kim J; Taira M; Zhan S; Sredni D; Kung HF
Laboratory of Biochemical Physiology, BRMP, NCI-FCRDC, NIH, Frederick, MD 21702-1201, USA.
Biochemical and biophysical research communications (UNITED STATES) Jul 6 1995, 212 (1) p212-9, ISSN 0006-291X Journal Code: 9Y8
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Injection of DN-BR mRNA encoding a dominant negative type I receptor for bone morphogenetic protein 4 (BMP4) converted prospective ectoderm into **neural** tissue in Xenopus animal cap explants, in the absence of expression of mesodermal marker genes. The injected caps expressed a general **neural** marker NCAM and the forebrain marker opsin. Coinjection of wild-type BMP4 receptor mRNA completely reversed the neuralization by DN-BR. No expression of known neuralizing factors, i.e., **noggin** and **follistatin** , was detected in the DN-BR-injected animal caps. Furthermore, neuralization elicited by **noggin** or 3m, a LIM domain mutant of Xlim-1, was substantially inhibited by co-injection of BMP4 mRNA. Since BMP4 is expressed in the prospective ectoderm during gastrulation, our results suggest that the ventralizing factor BMP4 acts also as a physiological inhibitor of neuralization in the development of Xenopus ectoderm.

5/3,AB/71 (Item 71 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08541463 95240743
Molecular mechanisms of tissue determination and pattern formation in amphibian embryos.
Tiedemann H; Tiedemann H; Grunz H; Knochel W
Institut fur Molekularbiologie und Biochemie, Freien Universitat, Berlin.
Die Naturwissenschaften (GERMANY) Mar 1995, 82 (3) p123-34, ISSN 0028-1042 Journal Code: NSW
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, ACADEMIC
Factors of the TGF-beta superfamily (activin, vegetalizing factor) and

the FGF family determine endoderm and mesoderm. The dorsoventral polarity of the mesoderm depends on additional factors (**BMP**-4, Wnt-8, **noggin**). Activin can directly activate gene transcription by signal transduction. Mesoderm is determined by factors prelocalized in the marginal zone. Its differentiation depends also on the animal ectoderm. **Neural** inducing factors have been partially purified. A masked neuralizing factor in the ectoderm is activated by induction of the ectoderm to the nervous system. Phorbolester can evoke neuralization signaling.

5/3,AB/72 (Item 1 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12715261 BIOSIS NO.: 200000468763
Evolutionary conservation of the presumptive **neural** plate markers AmphiSox1/2/3 and AmphiNeurogenin in the invertebrate chordate amphioxus.
AUTHOR: Holland Linda Z(a); Schubert M(a); Holland N D(a); Neuman T
AUTHOR ADDRESS: (a)Marine Biology Research Division, Scripps Institution of Oceanography, University of California at San Diego, La Jolla, CA, 92093-0202**USA
JOURNAL: Developmental Biology 226 (1):p18-33 October 1, 2000
MEDIUM: print
ISSN: 0012-1606
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Amphioxus, as the closest living invertebrate relative of the vertebrates, can give insights into the evolutionary origin of the vertebrate body plan. Therefore, to investigate the evolution of genetic mechanisms for establishing and patterning the neuroectoderm, we cloned and determined the embryonic expression of two amphioxus transcription factors, AmphiSox1/2/3 and AmphiNeurogenin. These genes are the earliest known markers for presumptive neuroectoderm in amphioxus. By the early neurula stage, AmphiNeurogenin expression becomes restricted to two bilateral columns of segmentally arranged **neural** plate cells, which probably include precursors of motor neurons. This is the earliest indication of segmentation in the amphioxus nerve cord. Later, expression extends to dorsal cells in the nerve cord, which may include precursors of sensory neurons. By the midneurula, AmphiSox1/2/3 expression becomes limited to the dorsal part of the forming **neural** tube. These patterns resemble those of their vertebrate and Drosophila homologs. Taken together with the evolutionarily conserved expression of the dorsoventral patterning genes, BMP2/4 and **chordin**, in nonneural and **neural** ectoderm, respectively, of chordates and Drosophila, our results are consistent with the evolution of the chordate dorsal nerve cord and the insect ventral nerve cord from a longitudinal nerve cord in a common bilaterian ancestor. However, AmphiSox1/2/3 differs from its vertebrate homologs in not being expressed outside the CNS, suggesting that additional roles for this gene have evolved in connection with gene duplication in the vertebrate lineage. In contrast, expression in the midgut of AmphiNeurogenin together with the gene encoding the insulin-like peptide suggests that amphioxus may have homologs of vertebrate pancreatic islet cells, which express neurogenin3. In addition, AmphiNeurogenin, like its vertebrate and Drosophila homologs, is expressed in apparent precursors of epidermal chemosensory and possibly mechanosensory cells, suggesting a common origin for protostome and deuterostome epidermal sensory cells in the ancestral bilaterian.

5/3,AB/73 (Item 2 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12700993 BIOSIS NO.: 200000454495
Involvement of **BMP**-4/msx-1 and FGF pathways in **neural** induction in the Xenopus embryo.
AUTHOR: Ishimura Akihiko; Maeda Ryu; Takeda Masatoshi; Kikkawa Mika; Daar Ira Owen; Maeno Mitsugo(a)
AUTHOR ADDRESS: (a)Department of Biology, Faculty of Science, Niigata University, 8050 Ikarashi-2, Niigata, 950-2181**Japan
JOURNAL: Development Growth & Differentiation 42 (4):p307-316 August, 2000
MEDIUM: print
ISSN: 0012-1592
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The msx homeodomain protein is a downstream transcription factor of the bone morphogenetic protein (**BMP**)-4 signal and a key regulator for **neural** tissue differentiation. Xmsx-1 antagonizes the dorsal expression of **noggin** and cerberus, as revealed by in situ hybridization and reverse transcription-polymerase chain reaction assays. In animal cap explants, Xmsx-1 and **BMP**-4 inhibit the **neural** tissue differentiation induced by **noggin** or cerberus. A loss-of-function study using the Xmsx-1/VP-16 fusion construct indicated that **neural** tissue formation was directly induced by the injection of fusion ribonucleic acid, although the expression of **neural** cell adhesion molecule (N-CAM) in the cap was less than that in the cap injected with tBR or **noggin**. In contrast to the single cap assay, unexpectedly, both **BMP**-4 and Xmsx-1 failed to inhibit neurulation in the ectodermal explants to which the organizer mesoderm was attached. The results of cell-lineage tracing experiments indicated that the **neural** cells were differentiated from the animal pole tissue where the excess RNA of either **BMP**-4 or Xmsx-1 was injected, whereas notochord was differentiated from the organizer mesoderm. **Neural** tissue differentiated from **BMP**-4-injected ectodermal cells strongly expressed posterior **neural** markers, such as hoxB9 and krox20, suggesting that the posterior **neural** cells differentiated regardless of the existence of the **BMP** signal. The introduction of a dominant-negative form of the fibroblast growth factor (FGF) receptor (XFD) into the ectodermal cells drastically reduced the expression of pan and posterior **neural** markers (N-CAM and hoxB-9) if co-injected with **BMP**-4 RNA, although XFD alone at the same dose did not shut down the expression of N-CAM in the combination explants. Therefore, it is proposed that an FGF-related molecule was involved in the direct induction of posterior **neural** tissue in the inducing signals from the organizer mesoderm in vivo.

5/3,AB/74 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12667135 BIOSIS NO.: 200000420637
The development of the avian vertebral column.
AUTHOR: Christ Bodo(a); Huang Ruijin; Wilting Joerg
AUTHOR ADDRESS: (a)Institute of Anatomy, University of Freiburg, D-79001, Freiburg**Germany
JOURNAL: Anatomy and Embryology 202 (3):p179-194 September, 2000
MEDIUM: print
ISSN: 0340-2061
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Segmentation of the paraxial mesoderm leads to somite formation. The underlying molecular mechanisms involve the oscillation of "clock-genes" like c-hairy-1 and lunatic fringe indicative of an implication of the Notch signaling pathway. The cranio-caudal polarity of each segment is already established in the cranial part of the segmental plate and accompanied by the expression of genes like Deltal, Mespl, Mesp2, Uncx-1, and EphA4 which are restricted to one half of the prospective somite. Dorsoventral compartmentalization of somites leads to the development of the dermomyotome and the sclerotome, the latter forming as a consequence of an epithelio-to-mesenchymal transition of the ventral part of the somite. The sclerotome cells express Pax-1 and Pax-9, which are induced by notochordal signals mediated by sonic hedgehog (Shh) and **noggin**. The craniocaudal somite compartmentalization that becomes visible in the sclerotomes is the prerequisite for the segmental pattern of the peripheral nervous system and the formation of the vertebrae and ribs, whose boundaries are shifted half a segment compared to the sclerotome boundaries. Sclerotome development is characterized by the formation of three subcompartments giving rise to different parts of the axial skeleton and ribs. The lateral sclerotome gives rise to the laminae and pedicles of the **neural** arches and to the ribs. Its development depends on signals from the notochord and the myotome. The ventral sclerotome giving rise to the vertebral bodies and intervertebral discs is made up of Pax-1 expressing cells that have invaded the perinotochordal space. The dorsal sclerotome is formed by cells that migrate from the dorso-medial angle of the sclerotome into the space between the roof plate of the **neural** tube and the dermis. These cells express the genes Msx1 and Msx2, which are induced by **BMP**-4 secreted from the roof plate, and they later form the dorsal part of the **neural** arch and the spinous process. The formation of the ventral and dorsal sclerotome requires directed migration of sclerotome cells. The regionalization of the paraxial mesoderm occurs by a combination of functionally Hox genes, the Hox code, and determines the segment identity. The development of the vertebral column is a consequence of a segment-specific balance between proliferation, apoptosis and differentiation of cells.

5/3,AB/75 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12646343 BIOSIS NO.: 200000399845
Characterization of **follistatin** isoforms in early Xenopus embryogenesis.
AUTHOR: Yamamoto Takamasa S; Iemura Shun-Ichiro; Takagi Chiyo; Shimasaki Shunichi; Ueno Naoto(a)
AUTHOR ADDRESS: (a)Department of Developmental Biology, National Institute for Basic Biology, 38 Nishigonaka, Okazaki, 444-8585**Japan
JOURNAL: International Journal of Developmental Biology 44 (4):p341-348 June, 2000
MEDIUM: print
ISSN: 0214-6282
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: **Follistatin** is expressed in Spemann's organizer in the Xenopus gastrula and mimics the activity of the organizer, inducing a **neural** fate directly in the ectoderm. We have previously shown that **follistatin** inhibits **BMP** activity through a direct interaction. In this study, we have characterized the localization and function of two **follistatin** isoforms to examine the functional differences between them. One notable difference, previously described,

is that the shorter form (xFSS or xFS319) but not the C-terminally extended long form (xFSL) associates with cell surface matrices. Here, we show that the spatial-temporal expression pattern of xFSL and xFSS is indistinguishable. Interestingly, however, xFSS was found to have a more potent inhibitory activity against **BMP**-4 than xFSL. Furthermore, using a surface plasmon resonance biosensor, xFSS was shown to have a higher binding capacity for **BMP** subtypes. The diffusion rates of xFSS and xFSL ectopically expressed in Xenopus embryos were similar. Taken together, our results suggest that the difference in **BMP** -inhibiting activity of the two **follistatin** isoforms is mainly attributable to a difference in their **BMP** binding properties rather than to their diffusion rates.

5/3,AB/76 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12640210 BIOSIS NO.: 200000393712
Nervous system morphogenesis in vertebrates.
AUTHOR: Hemmati-Brivanlou Ali(a)
AUTHOR ADDRESS: (a)Rockefeller University, 1230 York Avenue, New York, NY, 10021-6399**USA
JOURNAL: M-S (Medecine Sciences) 16 (2):p150-158 Feb., 2000
MEDIUM: print
ISSN: 0767-0974
DOCUMENT TYPE: Literature Review
RECORD TYPE: Abstract
LANGUAGE: French; Non-English
SUMMARY LANGUAGE: English

ABSTRACT: Molecular approaches used in the studies of embryonic **neural** development in the vertebrate embryos have started to unravel pathways involved in **neural** induction and patterning of the central nervous system. **Neural** induction begins with inhibition of **BMP**/GDF type of signaling on the dorsal ectoderm. Factors such as **noggin**, **chordin**, **follistatin** and cerebrus derived from the organizer mediate this inhibition and thus unveil **neural** fate in the dorsal side. Downstream of this inhibition, the activity of transcription factors such as SoxD and neurogenin have been implicated with the differentiation of mature neurons. Concomitant and following morphogenetic movements of the **neural** plate, differentiation of subtypes of neurons begins along the three axes of the **neural** tube. Antero-posterior differentiation is mediated by secreted factors such as FGF and Wnts as well as retinoic acid. The Hox code also subdivides the **neural** tube in different A-P gene expression domains and has been suggested to mediate cell identity. Ventral differentiation seems to be mediated by signaling cascades initiated by SHH originally from the notochord and later from the floor plate. HNF3beta, a transcription factor also seems to be involved in ventral differentiation. On the dorsal side both BMPs and Wnts signaling cascades have been implicated in the establishment of dorsal **neural** fates. Transcription factors such as Pax3 and 7 are also involved in this differentiation which ultimately will produce the roof plate, sensory neurons and dorsal interneurons. Right left assymetry seems to be mediated by lefty (also a member of the TGFbeta family), and the transcription factor ptx2. All these influences will ultimately allow the establishment of different fates in the embryonic nervous system.

5/3,AB/77 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12634401 BIOSIS NO.: 200000387903

Drm/**Gremlin** (CKTSF1B1) maps to human chromosome 15 and is highly expressed in [redacted]lt and fetal brain.
AUTHOR: Topol L Z; Modi W S; Koochekpour S; Blair D G(a)
AUTHOR ADDRESS: (a)NCI-FCRDC, Bldg. 469, Rm. 102, Frederick, MD, 21702-1201 **USA
JOURNAL: Cytogenetics and Cell Genetics 89 (1-2):p79-84 2000
MEDIUM: print
ISSN: 0301-0171
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: We have mapped and characterized the human homolog of Drm/**Gremlin** (CKTFS1B1), a member of a family of **BMP** antagonists that have been linked to both developmental and transformation-related functions. By screening a human cDNA library, we isolated a 3.3-kb cDNA containing the 552-bp region encoding the human DRM protein. CKTFS1B1 was localized on human chromosome 15q13fwdarwq15 by somatic cell hybrid analysis and, more precisely, using radiation hybrids, to a region of markers linked to SGNE1, secretory granule neuroendocrine protein 1 and RYR3, the rya-nodyne receptor 3. Northern blot analysis showed the presence of a single DRM-specific mRNA expressed in different human tissues, including brain, ovary, intestine and colon. In the brain, DRM expression is associated with the region localized around the internal capsule in the large subcortical nuclei. DRM appears to be predominantly expressed in normal cells and tissues, including normal neurons, astrocytes and fibroblasts. Interestingly, we detected DRM expression in normal cells obtained from several patients, but not in tumor cell lines established from the same patients. The data suggest that down-regulation of DRM is associated with tumor progression, and support the hypothesis that human DRM may play an important role during both neuroembryological development and carcinogenesis.

5/3,AB/78 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12576074 BIOSIS NO.: 200000329576
The organizer factors **Chordin** and **Noggin** are required for mouse forebrain development.
AUTHOR: Bachiller Daniel; Klingensmith John; Kemp C; Belo J A; Anderson R M ; May S R; McMahon J A; McMahon A P; Harland R M; Rossant J; De Robertis E M(a)
AUTHOR ADDRESS: (a)Department of Biological Chemistry, Howard Hughes Medical Institute, University of California, Los Angeles, CA, 90095-1662 **USA
JOURNAL: Nature (London) 403 (6770):p658-661 Feb. 10, 2000
MEDIUM: print
ISSN: 0028-0836
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: In mice, there is evidence suggesting that the development of head and trunk structures is organized by distinctly separated cell populations. The head organizer is located in the anterior visceral endoderm (AVE) and the trunk organizer in the node and anterior primitive streak. In amphibians, Spemann's organizer, which is homologous to the node, partially overlaps with anterior endoderm cells expressing homologues of the AVE markers cerberus, Hex and Hesx1 (refs 3-6). For mice, this raises the question of whether the AVE and node are independent of each other, as suggested by their anatomical separation,

or functionally interdependent as is the case in amphibians. Chordia and **Noggin** are secreted bone morphogenetic protein (**BMP**) antagonists expressed in the mouse node, but not in the AVE. Here we show that mice double-homozygous mutants that are for **chordin** and **noggin** display severe defects in the development of the prosencephalon. The results show that **BMP** antagonists in the node and its derivatives are required for head development.

5/3,AB/79 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12537451 BIOSIS NO.: 200000290953
Use of **follistatin** to modulate growth and differentiation factor 8 [GDF-8] and bone morphogenic protein 11 [**BMP**-11].
AUTHOR: Wood Clive R(a); Fitz Lori Jo
AUTHOR ADDRESS: (a)Boston, MA**USA
JOURNAL: Official Gazette of the United States Patent and Trademark Office Patents 1229 (3):pNo pagination Dec. 21, 1999
MEDIUM: e-file.
ISSN: 0098-1133
DOCUMENT TYPE: Patent
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Methods are provided for the modulation of the effects of GDF-8 and **BMP**-11, particularly on **neural** and muscular disorders administration of **follistatin** for treating **neural**, muscle, disorders which are characterized by an abnormality in the levels or activity of GDF-8 or **BMP**-11.

5/3,AB/80 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12475426 BIOSIS NO.: 200000228928
A **BMP** pathway regulates cell fate allocation along the sea urchin animal-vegetal embryonic axis.
AUTHOR: Angerer Lynne M(a); Oleksyn David W; Logan Catriona Y; McClay David R; Dale Leslie; Angerer Robert C
AUTHOR ADDRESS: (a)Department of Biology, University of Rochester, Rochester, NY, 14627**USA
JOURNAL: Development (Cambridge) 127 (5):p1105-1114 March, 2000
ISSN: 0950-1991
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: To examine whether a **BMP** signaling pathway functions in specification of cell fates in sea urchin embryos, we have cloned sea urchin BMP2/4, analyzed its expression in time and space in developing embryos and assayed the developmental consequences of changing its concentration through mRNA injection experiments. These studies show that BMP4 mRNAs accumulate transiently during blastula stages, beginning around the 200-cell stage, 14 hours postfertilization. Soon after the hatching blastula stage, BMP2/4 transcripts can be detected in presumptive ectoderm, where they are enriched on the oral side. Injection of BMP2/4 mRNA at the one-cell stage causes a dose-dependent suppression of commitment of cells to vegetal fates and ectoderm differentiates almost exclusively as a squamous epithelial tissue. In contrast, **NOGGIN**, an antagonist of BMP2/4, enhances differentiation of endoderm, a vegetal tissue, and promotes differentiation of cells

characteristic of the ciliated band, which contains neurogenic ectoderm. These findings support a model in which the balance of BMP2/4 signals produced by animal cell progeny and opposing vegetalizing signals sent during cleavage stages regulate the position of the ectoderm/endoderm boundary. In addition, BMP2/4 levels influence the decision within ectoderm between epidermal and nonepidermal differentiation.

5/3,AB/81 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12464191 BIOSIS NO.: 200000217693
Gene expression and pattern formation during early embryonic development in amphibians.
AUTHOR: Grunz Horst(a)
AUTHOR ADDRESS: (a)FB 9 Abteilung Zoophysiologie, Universitaet GH Essen, Universitaetsstr. 5, 45117, Essen**Germany
JOURNAL: Journal of Biosciences (Bangalore) 24 (4):p515-528 Dec., 1999
ISSN: 0250-5991
DOCUMENT TYPE: Manual
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Temporal and spatial gene expression and inductive interactions control the establishment of the body plan during embryogenesis in invertebrates and vertebrates. The best-studied vertebrate model system is the amphibian embryo. Seventy-five years after the famous organizer experiment of Hans Spemann and Hilde Mangold in 1924 our knowledge of the molecular mechanisms of the multi-step formation of embryonic axis has substantially improved. Although in the 30s and 40s the interest of many laboratories was focussed on **neural** induction (determination of the central nervous system), only crude factors from so-called heterogeneous inducers (liver, bone marrow, etc.,) could be isolated by the traditional biochemical techniques available at this time. An important breakthrough was the characterization and purification of a mesoderm inducing factor, the so-called vegetalizing factor (homologous to Activin) in highly purified from chicken embryos. Much later after the introduction of molecular techniques Vg1 and Activin (both belonging to the TGF-beta family) and FGFs could be identified as important factors for mesoderm formation. It was in the 90s that secreted neuralizing factors (**chordin**, **noggin**, **follistatin** and cerberus) could be detected, which are expressed at the dorsal side of the early embryo including the Spemann organizer. In contrast to the classical view, these proteins act as antagonists to factors like **BMP**-4 localized on the ventral side. Of special interest was the fact that in Drosophila sog, homologous to **chordin**, determines the ventral side, while dpp, homologous to **BMP**-4, participates in the formation of the dorsal side. These data of evolutionary conserved genes in both invertebrates and vertebrates support the view that they are descendents of common ancestors, the urbilateralia, living around 300 million years ago. The expression of those genes coding for secreted proteins is closely related to inductive interactions between cells and germ layers. Recently it was shown that planar signals are not sufficient to generate a specific anterior/posterior pattern during the primary steps of **neural** induction, i.e., formation of the central nervous system in amphibians.

5/3,AB/82 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12438831 BIOSIS NO.: 200000192333
CRIM1, a novel gene encoding a cysteine-rich repeat protein, is

developmentally regulated and implicated in vertebrate CNS development and organogenesis.
AUTHOR: Kolle G; Georgas K; Holmes G P; Little M H(a); Yamada T(a)
AUTHOR ADDRESS: (a)Centre for Molecular and Cellular Biology, University of Queensland, Brisbane, QLD, 4072**Australia
JOURNAL: Mechanisms of Development 90 (2):p181-193 Feb., 2000
ISSN: 0925-4773
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Development of the vertebrate central nervous system is thought to be controlled by intricate cell-cell interactions and spatio-temporally regulated gene expressions. The details of these processes are still not fully understood. We have isolated a novel vertebrate gene, CRIM1/Crim1, in human and mouse. Human CRIM1 maps to chromosome 2p21 close to the Spastic Paraplegia 4 locus. Crim1 is expressed in the notochord, somites, floor plate, early motor neurons and interneuron subpopulations within the developing spinal cord. CRIM1 appears to be evolutionarily conserved and encodes a putative transmembrane protein containing an IGF-binding protein motif and multiple cysteine-rich repeats similar to those in the **BMP**-associating **chordin** and sog proteins. Our results suggest a role for CRIM1/Crim1 in CNS development possibly via growth factor binding.

5/3,AB/83 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12407232 BIOSIS NO.: 200000160734
Noggin is a negative regulator of neuronal differentiation in developing neocortex.
AUTHOR: Li Weiwei; LoTurco Joseph J(a)
AUTHOR ADDRESS: (a)Department of Physiology and Neurobiology, University of Connecticut, U-156, Storrs, CT, 06269-4156**USA
JOURNAL: Developmental Neuroscience. 22 (1-2):p68-73 Jan.-April, 2000
ISSN: 0378-5866
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: Bone morphogenetic proteins (BMPs) trigger neuronal differentiation of neocortical precursors within the ventricular zone (VZ) (Li et al. (1998): J Neurosci 18:8853-8862). **BMP**-2/4 protein is concentrated at the VZ surface and BMPs rapidly promote the differentiation of neocortical precursors in both dissociated cell and explant cultures. **Noggin** binds to **BMP**-2/4 with high affinity, and prevents binding to cell surface receptors. In the present study, we used human recombinant **noggin** protein to determine whether endogenous **BMP**-2/4 triggers neuronal differentiation in dissociated cell culture. We find that **noggin** inhibits the differentiation of neocortical neurons: **noggin** decreases the number of MAP-2- and TUJ1-positive cells after 24 h of treatment, yet has no effect on either proliferation or cell survival. **Noggin** also significantly decreases neurite growth of MAP-2-positive cells. In addition, using Western blot analysis we show that **noggin** protein is present in developing cortex at E15. These results are consistent with previous results showing that endogenous BMPs trigger neuronal differentiation in the neocortical VZ and also indicate that a balance of **noggin** and **BMP** may regulate the differentiation of neocortical neurons in vivo.

5/3,AB/84 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12392444 BIOSIS NO.: 200000145946
Gradients of both **noggin** and **BMP** expression regulate cerebral cortical cell fate.
AUTHOR: Mabie P C(a); Mehler M F; Seto S; Kessler J A
AUTHOR ADDRESS: (a)Dept. of Neurol., Albert Einstein Coll. of Med., Bronx, NY, 10461**USA
JOURNAL: Society for Neuroscience Abstracts. 25 (1-2):p1287 1999
CONFERENCE/MEETING: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English

5/3,AB/85 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12391391 BIOSIS NO.: 200000144893
Noggin is a negative regulator of neuronal differentiation in neocortex.
AUTHOR: Li W(a); LoTurco J J(a)
AUTHOR ADDRESS: (a)Department of Physiology and Neurobiology, University of Connecticut, Storrs, CT, 06269**USA
JOURNAL: Society for Neuroscience Abstracts. 25 (1-2):p1029 1999
CONFERENCE/MEETING: 29th Annual Meeting of the Society for Neuroscience. Miami Beach, Florida, USA October 23-28, 1999
SPONSOR: Society for Neuroscience
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English
SUMMARY LANGUAGE: English

5/3,AB/86 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

12355522 BIOSIS NO.: 200000109024
Activin and bone morphogenetic proteins induce calcitonin gene-related peptide in embryonic sensory neurons in vitro.
AUTHOR: Ai Xingbin(a); Cappuzzello Jason(a); Hall Alison K(a)
AUTHOR ADDRESS: (a)Department of Neurosciences, Case Western Reserve University School of Medicine, Cleveland, OH, 44106-4975**USA
JOURNAL: Molecular and Cellular Neuroscience 14 (6):p506-518 Dec., 1999
ISSN: 1044-7431
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English

ABSTRACT: The neuropeptide calcitonin gene-related peptide (CGRP) expressed by one-third of rat dorsal root ganglion (DRG) neurons mediates pain sensation and vasodilation. The developmental regulation of CGRP is poorly understood, but may involve target-derived factors from skin or viscera. Few embryonic DRG neurons in defined culture express CGRP, indicating inductive signals are required. **Follistatin** blocked CGRP expression induced by serum or skin-conditioned medium, implicating transforming growth factor beta (TGFbeta) family members. Activin or bone

morphogenetic proteins (BMPs) 2, 4, or 6 stimulated CGRP expression in 60% of DRG neurons. Brief BMP4 application supported maximal CGRP induction, suggesting that BMP4 is a "switch" rather than a continuous modulator of neuropeptide phenotype. DRG expressed corresponding receptor subunits and exhibited Smad1 transcription factor nuclear translocation following **BMP** stimulation. **BMP** mRNAs were present in embryonic targets innervated by CGRP-expressing neurons. Thus, specific TGFbeta family members are candidate regulators of CGRP expression in sensory neurons.

5/3,AB/87 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11834196 BIOSIS NO.: 199900080305
Noggin induces a **neural** phenotype in ES cells, which is antagonized by **BMP**-4.
AUTHOR: O'Shea K S; Gratsch T E
AUTHOR ADDRESS: Univ. Michigan, Ann Arbor, MI 48109**USA
JOURNAL: Society for Neuroscience Abstracts 24 (1-2):p1526 1998
CONFERENCE/MEETING: 28th Annual Meeting of the Society for Neuroscience, Part 2 Los Angeles, California, USA November 7-12, 1998
ISSN: 0190-5295
RECORD TYPE: Citation
LANGUAGE: English

5/3,AB/88 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11746793 BIOSIS NO.: 199800527489
The **neural** inducer **chordin** and its downstream genes.
AUTHOR: Sasai Yoshiki(a)
AUTHOR ADDRESS: (a)Dep. Med. Embryol. Neurobiol., Inst. Frontier Med. Sch., Kyoto Univ., Kyoto**Japan
JOURNAL: Neuroscience Research Supplement (22):pS42 1998
CONFERENCE/MEETING: 21st Annual Meeting of the Japan Neuroscience Society and the First Joint Meeting of the Japan Neuroscience Society and the Japanese Society for Neurochemistry Tokyo, Japan September 21-23, 1998
SPONSOR: Japan Neuroscience Society
ISSN: 0921-8696
RECORD TYPE: Citation
LANGUAGE: English

5/3,AB/89 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

11726150 BIOSIS NO.: 199800507881
Somitogenesis controlled by **Noggin**.
AUTHOR: Tonegawa Akane; Takahashi Yoshiko(a)
AUTHOR ADDRESS: (a)Nara Inst. Sci. Technol., 8916-5 Takayama, Ikoma, Nara 630-0101**Japan
JOURNAL: Developmental Biology 202 (2):p172-182 Oct. 15, 1998
ISSN: 0012-1606
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In vertebrates, the segmented somites, which are the medial-most component in the paraxial mesoderm, are the entity giving rise to the axial bones and skeletal muscles. We previously demonstrated that the

mechanism that distinguishes the somite from the more lateral mesoderm (lateral plate) involves different levels of BMP-4 activity which is highest in the lateral plate. We report that **Noggin**, an antagonist of **BMP**-4, is expressed in the presumptive somite and appears to control effective levels of **BMP**-4 to differentiate somitic mesoderm from the lateral plate. When **Noggin**-producing cells were implanted into the presumptive lateral plate, they produced ectopic somites that were respecified from the lateral plate precursors. These somites exhibited no mediolateral (M-L) polarity, but acquired it when implanted **Noggin** was eliminated. Thus, in normal embryogenesis no or low **BMP**-4 activity realized by **Noggin** specifies the somites in the medial-most portion of the paraxial mesoderm, and then **BMP**-4 emanating from the lateral plate subsequently establishes the M-L polarity in the somites.